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Case Report

Uterine Bleeding in a Postmenopausal Patient: Debut of a Granulosa Cell Tumor

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Abstract

Granulosa cell tumor (GCT) belongs to the group of sex cord-stromal tumors and represents approximately 2 - 5% of cases. GCTs are divided into two subtypes: the adult type, which accounts for 95% of all GCTs, and the juvenile type, accounting for the remaining 5%. The adult subtype most commonly occurs in patients between 50 and 54 years old, while the juvenile subtype usually develops before puberty.

The distinct feature of GCTs is their malignant potential, evidenced by long-term recurrences. Herein, we report a case of an adult-type GCT in a 62-year-old female patient, and provide a detailed analysis of its clinical presentation, diagnosis and treatment. The patient was successfully treated with primary debulking surgery and adjuvant chemotherapy.

The importance of an early diagnosis and long-term follow-up is emphasized, given the risk of recurrence. This case provides a comprehensive view of GCT management and highlights the need for a thorough evaluation and an interdisciplinary approach for an effective treatment of this uncommon ovarian neoplasm.

Keywords: *Granulosa Cell Tumor; Ovarian Cancer; Sex Cord-Stromal Tumor; Hyperestrogenism*

Introduction

Granulosa cell tumors (GCTs) are a unique entity within the wide spectrum of ovarian neoplasms, accounting for approximately 2 - 5% of primary ovarian neoplasms. These tumors, which belong to the group of sex cord-stromal tumors, are characterized not only for being relatively rare, but also for their functional capacity to produce steroid hormones, mainly estrogens [1,2].

GCTs are divided into two main subtypes: the adult type, accounting for about 95% of cases and typically occurring between the ages of 50 and 54 years, and the juvenile type, which represents the remaining 5% and usually occurs before puberty [3,4]. Adult GCTs comprise the majority (70%) of sex cord-stromal tumors [5].

Excessive hormone production of estrogen may lead to a range of clinical manifestations, which vary depending on the time of tumor presentation [3].

The diagnosis of GCT is complex and requires a combination of imaging studies, specific tumor markers and, finally, confirmatory histopathological analysis. Elevated levels of inhibin and anti-müllerian hormone (AMH) along with clinical and radiological features are essential to differentiate GCTs from other ovarian tumors. They are usually diagnosed at an early stage of the disease, with overall 5-year survival rates above 90% after treatment. However, these tumors require continuous follow-up, as recurrences have been reported more than a decade after clinical remission [6]. The documented median time to recurrence is usually 4 to 6 years following initial diagnosis [7].

This paper focuses on the distinctive clinical presentation of a case of adult GCT, complemented by a detailed literature review. The aim of this work is to shed some light on this rare entity and highlight the importance of an early diagnosis and proper management to improve the prognosis and quality of life of patients with GCTs.

Case Report

A 62-year-old female presented to the gynecological endocrinology division of this hospital due to a single episode of postmenopausal genital bleeding accompanied by breast tenderness of one-month duration. The patient had a history of 3 pregnancies and 3 miscarriages, and had undergone surgery for a cerebellar cavernoma in 2013 and a right adnexectomy for a dermoid cyst at the age of 40. Her last menstrual period had been at the age of 50.

On physical examination, the patient had normal blood pressure, a body weight of 59.9 kg, a height of 1.61 m, a waist circumference of 79 cm and a body mass index of 23.12 kg/m^2. She had no signs of hyperandrogenism. On gynecological examination, the vulva appeared normal and estrogenized, without clitoromegaly. Speculoscopy showed a healthy cervix with presence of cervical mucus. No bleeding at the time of consultation. A transvaginal ultrasound was requested, and a Pap smear was collected.

The patient returned with a hypotrophic Pap smear, negative for intraepithelial lesion. The transvaginal Doppler ultrasound showed a uterus in anteversion and anteflexion, with echogenic central endometrial line of 1.3 mm, absence of the right ovary (surgical history), left ovary measuring 52 x 34 mm with a heterogeneous mass of solid appearance and irregular borders measuring 42 x 32 mm, consistent with ovarian blastoma. Douglas' pouch was clear. The left ovarian mass was evaluated with color Doppler and power-angio, showing moderate peripheral and central vessels with low-resistance arterial flow (RI: 0.29-0.35), with indices suggestive of increased vascularization and flow patterns of new blood vessel growth (See figure 1). Histological evaluation was suggested, along with a correlation with Ca 125 and further evaluation with more sophisticated imaging studies (magnetic resonance imaging, MRI).

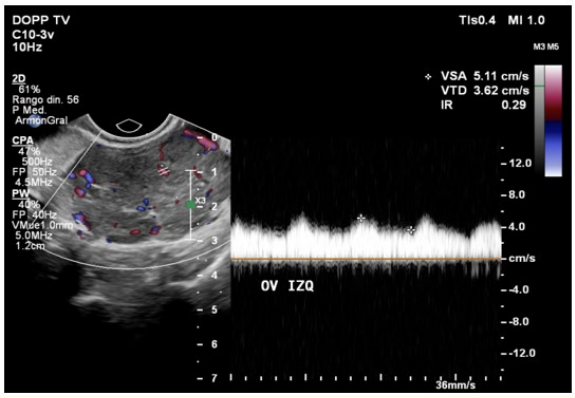

Figure 1: *Doppler ultrasound shows a solid heterogeneous left ovarian mass with low RI.*

Tumor markers and hormone measurement tests were ordered because of the symptoms prior to bleeding (breast tenderness) and the presence of cervical mucus. The following results were obtained using electrochemiluminescence immunoassay analyzer (ECLIA): luteinizing hormone (LH): 11.6 mIU/ml, follicle-stimulating hormone (FSH): 2.2 mIU/ml, estradiol (E2): 122.1 pg/mL, CA-125: 16.3 U/ml, CEA: < 0.5 ng/ml (See table 1).

Hormone marker	Preoperative value	Postoperative value	Postmenopausal normal values
LH mIU/mL	11.6	49.0	7.7 – 58.5
Estradiol (E2) pg/mL	122.1	< 26.0	< 25.0
FSH mIU/mL	2.2	81.4	25.8 -134.8
Inhibin pg/mL	4480	< 10	< 10 pg/mL

Table 1

With a suspected diagnosis of GCT, inhibin and AMH testing was requested. The patient was only able to undergo inhibin testing, with reported levels of 4480 pg/mL (Enzyme-linked immunosorbent assay (ELISA) reference value < 10).

The intravenous contrast-enhanced MRI report of the abdomen and pelvis showed a uterus in anteversion and anteflexion, with a 3-mm thick endometrium and, at retrouterine level on the left side, a lobulated mass of solid nature and well-defined borders measuring 47 x 30 mm, which appeared predominantly hyperintense and heterogeneous on T2-weighted sequences, with marked restricted diffusion and mildly heterogeneous enhancement after contrast administration. The lesion was categorized as O-RADS 5. There was free fluid within the true pelvis. The study was otherwise unremarkable (See figure 2 and 3).

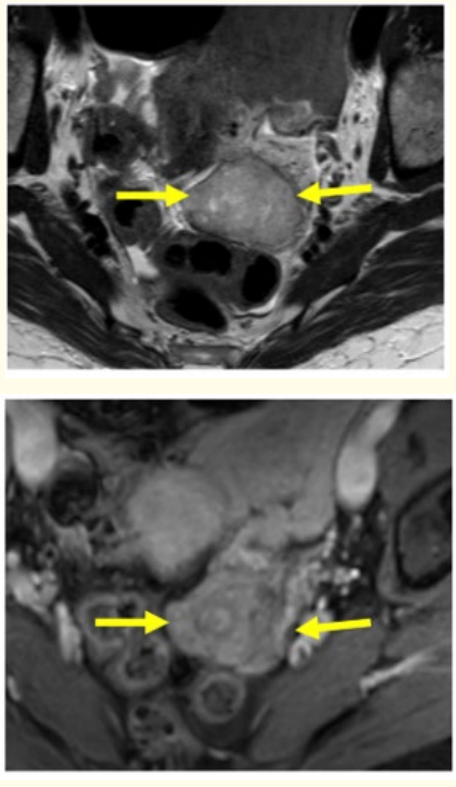

Figure 2: *Axial T2 weighted image shows a lobulated mass with mildly heterogeneous high signal intensity. Axial postcontrast T1-weighted image shows heterogeneous enhancement.*

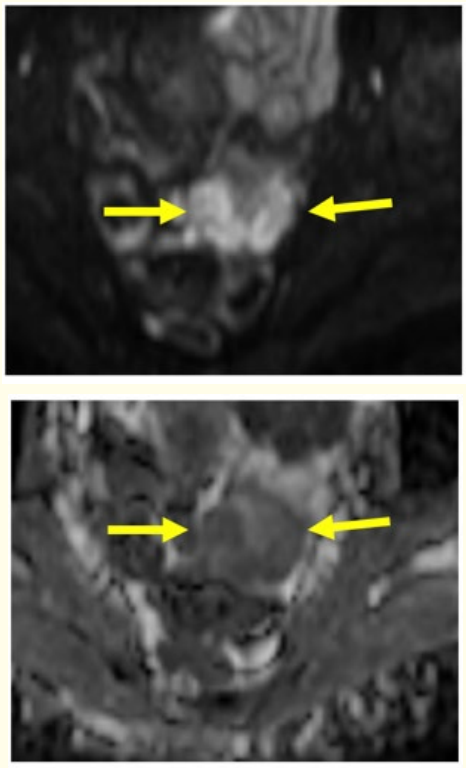

Figure 3: *Diffusion-weighted image shows hyperintense signal and apparent diffusion coefficient map depicts low signal in keeping with diffusion restriction.*

Considering these complementary studies, a decision was made to perform an exploratory laparotomy with a suspected diagnosis of ovarian neoplasm, probably granulosa cell tumor. The patient underwent total hysterectomy with bilateral salpingo-oophorectomy, omentectomy, multiple biopsies and peritoneal fluid sampling. The deferred pathology report confirmed a 4-cm adult-type granulosa cell tumor with an intact ovarian capsule and a 2-mm peritubal GCT focus in the left fallopian tube, endometrial hyperplasia without atypia, omentectomy and biopsies with no presence of metastasis and negative peritoneal fluid cytology.

Before completing one month after surgery, repeat hormone and inhibin testing was requested. Inhibin levels had normalized and hormone levels had returned to postmenopausal ranges (See table 1).

The patient subsequently completed 6 sessions of chemotherapy with carboplatin and paclitaxel. She is currently on joint follow-up by the oncology and gynecology teams. She has no symptoms of recurrence and maintains a good quality of life. Follow-up will continue by biannual imaging and inhibin measurements to monitor for signs of recurrence, given the nature of GCTs.

Discussion

The case of GCT reported herein constitutes a rare ovarian neoplasm. The low prevalence of this type of tumor makes diagnosis challenging due to its varied clinical presentation. As with epithelial ovarian cancer, the presenting symptoms are usually nonspecific

with abdominal pain and distention. Since GCTs are functional tumors with the ability to produce steroid hormones, they usually present with symptoms of estrogen excess [8]. Juvenile GCT may present with precocious development of secondary sex characteristics, while in the adult subtype, symptoms will vary depending on whether the tumor occurs during the premenopausal or postmenopausal period. In the premenopausal period, it may present with abnormal uterine bleeding, amenorrhea, or, rarely, infertility due to abnormal inhibin secretion. In the postmenopausal period, it presents with abnormal vaginal bleeding [9]. Since GCTs are associated with endocrine clinical manifestations due to hormone production, most patients are diagnosed at early stages (78 - 91%) and generally show a better prognosis than women with other types of ovarian cancer [10-12]. Moreover, exposure to endogenous estrogens can lead to endometrial alterations, including hyperplasia and even endometrial carcinoma [6]. Our patient experienced a single episode of genital bleeding, and neither the gynecological ultrasound nor the MRI scan revealed endometrial thickening, in spite of the fact that the pathology report indicated the presence of endometrial hyperplasia without atypia.

The diagnosis of GCT is a multifaceted process that requires a combination of imaging studies and tumor markers, confirmed by histopathological and immunohistochemical analysis [5,6,8]. GCTs arise from proliferating normal preovulatory granulosa cells (GCs) and retain several characteristics of these GCs; thus, in addition to secreting large amounts of estrogen, they secrete proteins such as inhibin, which constitutes a specific tumor marker. However, it has been reported that not all GCTs show increased serum levels of inhibin and that patients with epithelial ovarian cancer may rarely show an increase in this glycoprotein [4]. Anti-müllerian hormone (AMH), like inhibin, is also produced by granulosa cells, has been found to be elevated in 8 out of 9 patients with GCT progression and undetectable in 10 out of 11 patients with clinical remission, suggesting that it might be considered an effective marker for the diagnosis and follow-up of these tumors. However, its application for clinical use is limited. A mutation in the FOXL2 transcription factor gene has been identified in approximately 97% of GCTs; this is considered a typical molecular characteristic of these tumors [6,13]. In our patient, hormone levels and high serum inhibin levels led to suspicion of GCT.

The pathology report confirmed a 4-cm adult GCT with an intact ovarian capsule, but with a 2-mm peritubal focus in the left fallopian tube. No metastatic sites were observed in the omentum or other abdominal structures; only the left fallopian tube was affected. Surgery was followed by a significant decrease in serum estradiol levels and concomitant increases in LH and FSH levels, consistent with the patient's postmenopausal state. However, complete remission cannot be concluded on the basis of these hormone values only, without considering postoperative inhibin levels and performing additional imaging studies to detect potential recurrence or residual mass.

Surgery remains the mainstay of treatment for GCT, with surgical options varying according to the patient's age and reproductive desires. For postmenopausal women, hysterectomy with bilateral adnexectomy is preferred, while for younger patients, conservative surgery is considered. The decision to add adjuvant chemotherapy or radiotherapy depends on the tumor size and stage, further complicating therapeutic management. As a general rule, adjuvant chemotherapy is reserved for extraovarian spread or tumor recurrence [14,15]. In our patient, tubal spread led to the decision of administering postoperative chemotherapy.

In contrast to epithelial ovarian cancers, late relapses are common in GCTs even after a five-year period. For this reason, despite the generally favorable prognosis of GCTs, the propensity to recurrence highlights the need for a long-term follow-up. Tumor markers for GCTs, namely inhibin, AMH and estradiol, can be useful not only for early diagnosis but also for the postoperative follow-up of these women [7,13].

This case highlights the importance of evaluating factors such as tumor size, the presence of residual mass and tumor staging for an accurate prognosis.

In the clinical setting, this case emphasizes the importance of maintaining a high index of suspicion for GCT, especially in women presenting with symptoms related to hyperestrogenism. Multidisciplinary cooperation among gynecologists, imaging specialists,

oncologists, and pathologists is essential for an accurate diagnosis and effective treatment. Furthermore, the rarity of GCT and its varied clinical presentation reinforces the need for continuous training for healthcare professionals.

Conclusion

The management of this case of GCT has exposed the challenges inherent to the rarity of this ovarian neoplasm. The infrequent occurrence of GCTs and their varied clinical presentation underscore the importance of careful consideration in the presence of symptoms associated with hyperestrogenism.

The suspected diagnosis was based on a combination of symptoms of hyperestrogenism, with consistent ovarian imaging findings and inhibin testing, but diagnosis confirmation was provided by pathology examination. Surgery remains the mainstay of treatment, and the choice between conservative and more radical surgery depends on the patient's age and reproductive desires.

Long-term follow-up is essential due to the propensity for recurrences, even decades after surgery. Interdisciplinary cooperation among specialists and continuous education are vital for improving early detection and effective management of GCT.

This case provides valuable lessons for clinical practice, encouraging healthcare professionals to maintain a high suspicion for GCT in cases of hyperestrogenism. Continuous research in this field and customization of treatment strategies are essential for further improvement of the understanding and management of this unique clinical entity.

Ultimately, this analysis of a GCT case highlights the need for comprehensive and personalized patient care, recognizing the uniqueness of this ovarian neoplasm within the broader spectrum of gynecological diseases.

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