

## Endometrial Carcinoma Associated with Ovarian Granulosa Cell Tumors – A Case Report

NICOLAE BACALBASA<sup>1</sup>, CLAUDIA STOICA<sup>2</sup>, ILEANA POPA<sup>3</sup>, GRATIELA MIREA<sup>2</sup> and IRINA BALESCU<sup>4</sup>

<sup>1</sup>Obstetrics and Gynecology Department Carol Davila University of Medicine and Pharmacy, Bucharest, Romania;

<sup>2</sup>General Surgery Department, Ilfov County Hospital, Bucharest, Romania;

<sup>3</sup>Pathology Department Coltea Clinical Hospital, Bucharest, Romania;

<sup>4</sup>General Surgery Department, Ponderas Hospital, Bucharest, Romania

**Abstract.** Ovarian granulosa cell tumors represent uncommon neoplasms with estrogen-secreting capacity. Due to their association with persistently increased levels of estrogen, modifications of the endometrial tissue ranging from hyperplasia to malignant degeneration may be encountered. We present the case of a 65-year-old patient who presented for post-menopausal vaginal bleeding. The endometrial biopsy raised the suspicion of an atypical endometrial hyperplasia and the patient was submitted to surgery. Histopathological studies of the specimen of total hysterectomy with bilateral adnexectomy revealed the presence of a well-differentiated endometrial carcinoma associated with a granulosa cell tumor of the ovary. In conclusion whenever a modified aspect of the endometrium is found preoperatively, attention should be given on other possible underlying modifications and a radical approach should be taken in consideration.

Ovarian granulosa cell tumors represent uncommon neoplasms arising from the ovarian sex-cord stromal cells, and account for 2-5% of all ovarian cancer (1-3). Based on clinical and histopathological studies, these tumors are classified as juvenile and adult granulosa cell tumors (4). The main characteristic of these tumors is their hormone-secreting capacity, nearly all of them being capable of synthesizing estradiol (4). Due to this particularity, ovarian granulosa cell tumors are responsible for the iso-sexual precocious pseudopuberty in young girls (5), while in older

patients, abnormal vaginal bleeding, abdominal swelling and even abnormal palpable masses in the lower abdomen can be seen (4). Most tumors are large, solid or cystic, with slow growth and tendency for late recurrence (1, 4, 6). When it comes to their hormonal activity, estradiol has been advocated as a true tumor marker for these neoplasias (4, 7). However, the estradiol concentration is not a reliable marker of disease activity, no significant correlation has been established between it and the presence of bulky disease (8, 9). Despite this, high hormonal levels can be associated with other significant modifications of estrogen-sensitive tissues, such as endometrial tissues. Prolonged endometrial exposure to high estrogen levels are responsible for pathological modifications ranging from endometrial hyperplasia to endometrial cancer (10, 11). Most often, malignant endometrial degeneration will comprise well-differentiated endometrioid adenocarcinoma; in rare cases, another pathological pathway might be incriminated, unrelated to estrogen stimulation, leading to development of serous carcinoma. The differential diagnosis between the two histopathological sub-types can be provided by the presence of mutation of the *p53* tumor-suppressor gene, which is uncommon in endometrial carcinoma but is usually associated with serous carcinoma (12).

### Case Report

A 65-year-old patient presented for pelvic pain and reported two episodes of vaginal bleeding. The local examination showed no modifications of the uterine cervix; however, the vaginal tract revealed the presence of a tumor at the level of the left Douglas pouch. Papanicolau test excluded any microscopic modification of the uterine cervix, while transvaginal ultrasonography revealed the presence of an enlarged left adnexa measuring 12x8 cm, with a solid aspect associated with an enlarged endometrium. Laboratory tests including carcinoembryonic antigen and  $\alpha$ -fetoprotein were normal. The patient was submitted to endometrial biopsy,

This article is freely accessible online.

Correspondence to: Nicolae Bacalbaşa, Dimitrie Racoviţă Street, no. 2, Bucharest, Romania. Tel: +40 723540426, e-mail: nicolae\_bacalbasa@yahoo.ro

Key Words: Endometrial carcinoma, granulosa cell tumor of the ovary, total hysterectomy with bilateral adnexectomy.

which confirmed the presence of an endometrial hyperplasia with rare atypia; the patient was submitted to surgery. Intraoperatively, a large solid ovarian tumor entirely deforming the left adnexa was found, with no other macroscopic modifications. The patient was submitted to radical hysterectomy with bilateral adnexectomy, and pelvic and para-aortic lymph node dissection.

The histopathological studies revealed the presence of an adult ovarian granulosa cell tumor (Figure 1A) in the left ovary associated with a well-differentiated endometrioid adenocarcinoma (Figure 2). Microscopical evaluation revealed a diffuse growth pattern of adult granulosa cell tumor, with low mitotic activity of 1-2 mitoses per 10 high-power fields, with no surface involvement. The uterine body presented lesions of complex hyperplasia with cellular atypia associated with the presence of a locally well-differentiated invasive glandular process involving less than 50% of the myometrial depth. Estrogen receptors were present in up to 50% of tumoral cells, while progesterone receptors were found in 15%. The ovarian tumor stained positively for calretinin and inhibin (Figure 1B and C).

The postoperative course was uneventful, the patient being discharged on the sixth postoperative day. Postoperatively, the patient received no adjuvant treatment and remains free of recurrent disease at two-year follow-up.

## Discussion

Ovarian granulosa cell tumor represents the most common estrogen-secreting ovarian tumor followed by thecoma, both being considered as feminizing mesenchymomas of the ovary (13). In pre-pubertal patients, the main modifications consist of iso-sexual pseudoprecocity, with early development of secondary sexual characteristics, while in adults, the most common manifestation consists of menometrorrhagia, and only in isolated cases, amenorrhea. The adult tumor sub-type is most often found in post-menopausal women and is responsible for vaginal post-menopausal bleeding, associated with breast tenderness and diffuse pelvic pain (4, 5, 14, 15). In order to reach the right diagnosis, an endometrial biopsy is required; most commonly, endometrial hyperplasia exists; however, it seems that up to one-third of the specimens are associated with the presence of endometrial atypia. The natural progression of the disease is through low-grade endometrial endometrioid adenocarcinoma, which is reported in 5% up to 20% of cases. Less commonly, a serous adenocarcinoma will develop; however, it seems that is more likely to be related to the presence of *p53* mutation than to an excess of estrogen (6, 12, 16, 17). In patients with ovarian granulosa cell tumor, a four-fold increased incidence of breast cancer has also been reported (18).

In order to determine the most important prognostic factors which might predict the association with endometrial cancer, Ottolina *et al.* conducted a retrospective study involving 150 patients with adult granulosa cell tumors of the ovary. They demonstrated that endometrial carcinoma was most often present in symptomatic patients ( $p=0.001$ ) over 40 years of age or post-menopausal ( $p<0.001$ ) (19).

However, it seems that not only estrogen synthesis is responsible for the endometrial cancer in these patients. Another associated factor is the presence of steroid hormones (20, 21), while the presence of progesterone has an antagonistic action by down-regulating estrogen receptors and enhancing the conversion of estradiol to the less active estrone by increasing the activity of  $17\beta$ -hydroxysteroid dehydrogenase (19).

When it comes to the most important prognostic factors of women diagnosed with ovarian granulosa cell tumors, it seems that prognosis is strongly influenced by the initial stage at diagnosis, followed by the integrity of the ovarian capsule and the dimensions of the tumor. For patients diagnosed with early stages of the disease, one of the most important factors predicting the recurrence rate and overall survival remains the presence of nuclear atypia. A significant association between the presence of nuclear atypia and time to recurrence also exists: tumors which develop early recurrence usually have a higher rate of nuclear atypia, of up to 77%, while those with late recurrence present nuclear atypia in up to 33% of cases (4, 22, 23).

Regarding the most adequate therapeutic protocol, endometrial biopsy should be a rule in order to determine if any endometrial modifications have already occurred. In patients younger than 40 years with normal-appearing endometrium, desiring preservation of reproductive function, unilateral adnexectomy and close follow-up can be attempted, while in patients older than 40 years, total abdominal hysterectomy with bilateral adnexectomy should be the rule (4).

For the use of adjuvant radiotherapy, results are still conflicting. Irradiation has been used both as adjuvant treatment following surgery, and for recurrent disease. However, there is no randomized study assessing the role of adjuvant radiotherapy; although there are studies which demonstrate an improved rate of survival in newly-diagnosed patients or those with recurrent disease, others failed to demonstrate any benefit (6, 10, 24, 25). Concerning the necessity for performing adjuvant chemotherapy, the main indications for patients diagnosed with an early stage of the disease are the presence of large tumors with high mitotic index or ruptured capsule, while the main chemotherapeutic protocols include cisplatin, vinblastine, bleomycin or bleomycin, etoposide, cisplatin regimens (4, 26).

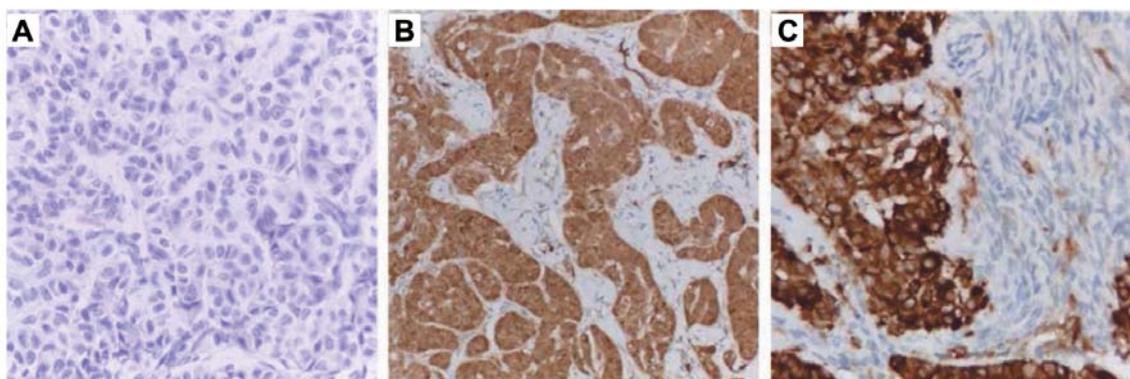


Figure 1. Ovarian granulosa cell tumor – hematoxylin-eosin stain (A), calretinin-positive (B) and inhibin-positive (C). Original magnification, A, B:  $\times 20$ ; C:  $\times 40$ .

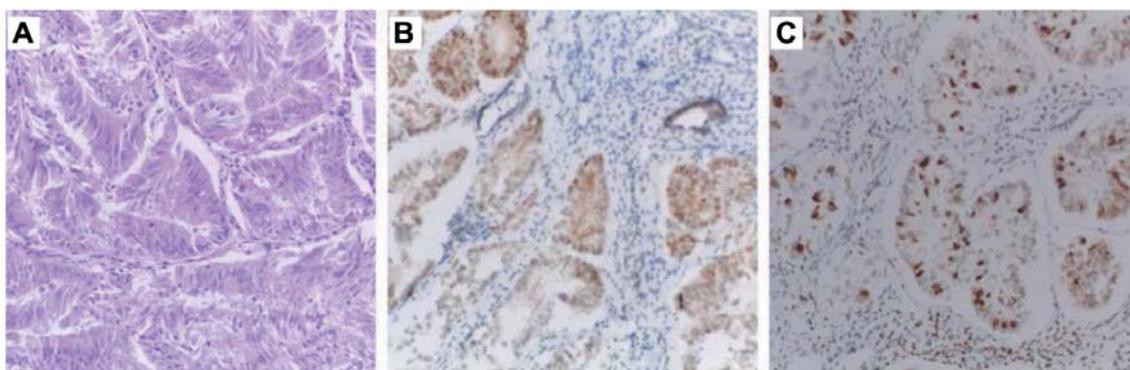


Figure 2. Endometrial adenocarcinoma – hematoxylin-eosin stain (A), positivity for estrogen receptor in 50% of the tumor cells (B), and for progesterone receptor in 15% of the tumor cells (C). Original magnification,  $\times 20$ .

## Conclusion

Concomitant adult ovarian granulosa cell tumor and endometrial hyperplasia or even endometrial cancer is not an uncommon situation, the relationship between the two neoplasias being established by a high level of estrogen produced by a hyperactive ovary. Due to this fact, endometrial biopsy is mandatory; whenever a modified aspect of the endometrium is found, the standard therapeutic protocol consists of total radical hysterectomy with bilateral adnexectomy.

## Acknowledgements

This work received financial support through the project entitled "CERO – Career profile: Romanian Researcher", grant number POSDRU/159/1.5/S/135760, cofinanced by the European Social Fund for Sectorial Operational Programme Human Resources Development 2007-2013.

## References

- 1 Evans AT, III, Gaffey TA, Malkasian GD Jr. and Annegers JF: Clinicopathologic review of 118 granulosa and 82 theca cell tumors. *Obstet Gynecol* 55: 231-238, 1980.
- 2 Fox H, Agrawal K and Langley FA: A clinicopathologic study of 92 cases of granulosa cell tumor of the ovary with special reference to the factors influencing prognosis. *Cancer* 35: 231-241, 1975.
- 3 Unkila-Kallio L, Tiitinen A, Wahlstrom T, Lehtovirta P and Leminen A: Reproductive features in women developing ovarian granulosa cell tumour at a fertile age. *Hum Reprod* 15: 589-593, 2000.
- 4 Pectasides D, Pectasides E and Psyrris A: Granulosa cell tumor of the ovary. *Cancer Treat Rev* 34: 1-12, 2008.
- 5 Vassal G, Flamant F, Caillaud JM, Demeocq F, Nihoul-Fekete C and Lemerle J: Juvenile granulosa cell tumor of the ovary in children: a clinical study of 15 cases. *J Clin Oncol* 6: 990-995, 1988.
- 6 Bjorkholm E and Silfversward C: Prognostic factors in granulosa-cell tumors. *GynecolOncol* 11: 261-274, 1981.

- 7 Kaye SB and Davies E: Cyclophosphamide, adriamycin, and cisplatinum for the treatment of advanced granulosa cell tumor, using serum estradiol as a tumor marker. *Gynecol Oncol* 24: 261-264, 1986.
- 8 Lappohn RE, Burger HG, Bouma J, Bangah M, Krans M and de Bruijn HW: Inhibin as a marker for granulosa-cell tumors. *N Engl J Med* 321: 790-793, 1989.
- 9 Rey RA, Lhomme C, Marcillac I, Lahlou N, Duvillard P, Josso N and Bidart JM: Antimullerian hormone as a serum marker of granulosa cell tumors of the ovary: comparative study with serum alpha-inhibin and estradiol. *Am J Obstet Gynecol* 174: 958-965, 1996.
- 10 Evans AT, III, Gaffey TA, Malkasian GD Jr. and Annegers JF: Clinicopathologic review of 118 granulosa and 82 theca cell tumors. *Obstet Gynecol* 55: 231-238, 1980.
- 11 Stenwig JT, Hazekamp JT and Beecham JB: Granulosa cell tumors of the ovary. A clinicopathological study of 118 cases with long-term follow-up. *Gynecol Oncol* 7: 136-152, 1979.
- 12 Lax SF: Molecular genetic pathways in various types of endometrial carcinoma: from a phenotypical to a molecular-based classification. *Virchows Arch* 444: 213-223, 2004.
- 13 Young, R, Scully, R: Sex Cord-Stromal, Steroid Cell, and Germ Cell Tumors of the Ovary *Glob. libr. women's med.*, (ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10249.
- 14 Busquets M, Gonzalez-Bosquet E, Muchart J, Rovira C and Laila JM: Granulosa cell tumor and endometrial cancer: a case report and review of the literature. *Eur J GynaecolOncol* 31: 575-578, 2010.
- 15 Alikhan M and Gwin K: An update regarding the effects of hormones on the endometrium: practical considerations for the surgical pathologist. *Diagnostic Histopathology* 19(7): 245-251, 2013.
- 16 Aboud E, Crow J and Gordon H: Sex cord-stromal tumours of the ovary – a 25-year review. *J ObstetGynaecol* 17: 554-556, 1997.
- 17 Rabban JT, Gupta D, Zaloudek CJ and Chen LM: Synchronous ovarian granulosa cell tumor and uterine serous carcinoma: a rare association of a high-risk endometrial cancer with aneustrogenic ovarian tumor. *GynecolOncol* 103: 1164-1168, 2006.
- 18 Ohel G, Kaneti H and Schenker JG: Granulosa cell tumors in Israel: a study of 172 cases. *GynecolOncol* 15: 278-286, 1983.
- 19 Ottolina J, Ferrandina G, Gadducci A, Scollo P, Lorusso D, Giorda G, Breda E, Savarese A, Candiani M, Zullo F and Mangili G: Is the endometrial evaluation routinely required in patients with adult granulosa cell tumors of the ovary? *GynecolOncol* 136: 230-234, 2015.
- 20 Sachdev D and Yee D: Disrupting insulin-like growth factor signaling as a potential cancer therapy. *Mol Cancer Ther* 6: 1-12, 2007.
- 21 Gadducci A and Genazzani AR: Steroid hormones in endometrial and breast cancer. Review. *Eur J GynaecolOncol* 18: 371-378, 1997.
- 22 Miller BE, Barron BA, Wan JY, Delmore JE, Silva EG and Gershenson DM: Prognostic factors in adult granulosa cell tumor of the ovary. *Cancer* 79: 1951-1955, 1997.
- 23 Kietlinska Z, Pietrzak K and Drabik M: The management of granulosa-cell tumors of the ovary based on long-term follow up. *Eur J GynaecolOncol* 14 *Suppl*: 118-127, 1993.
- 24 Schwartz PE and Smith JP: Treatment of ovarian stromal tumors. *Am J ObstetGynecol* 125: 402-411, 1976.
- 25 Diddle AW: Granulosa- and theca-cell ovarian tumors: prognosis. *Cancer* 5: 215-228, 1952.
- 26 Pectasides D, Alevizakos N and Athanassiou AE: Cisplatin-containing regimen in advanced or recurrent granulosa cell tumours of the ovary. *Ann Oncol* 3: 316-318, 1992.

*Received May 27, 2015*

*Revised July 16, 2015*

*Accepted July 20, 2015*