Preserving fertility in patients with granulosa cell tumors of the ovary

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Summary

Granulosa cell tumors of the ovary are rare ovarian neoplasms developing from ovarian stromal cells. They are characterized by insidious growth, low malignancy potential, and late recurrence. Due to the production of estrogen by these tumors, the frequent symptoms that occur in these patients develop as a result of hyperestrogenism. Standard treatment involves surgery in all patients. Fertility-sparing surgery is considered safe in young patients only in case of early-stage IA and IC tumors, where it is necessary to perform a unilateral salpingo-oophorectomy and complete staging. Surgical staging includes peritoneal washing, multiple peritoneal biopsies, omental biopsy, and biopsy of any suspicious area.

Key words: Ovarian granulosa cell tumor; Fertility-sparing surgery in patients with granulosa cell tumors.

Introduction

Granulosa cell tumors (GCT) originate from granulosa of the ovarian stroma and are classified as sex-cord stromal tumors [1]. GCT comprise only 3-5% of all ovarian tumors but are the most common subtype of ovarian sex-cord tumor (70%) [2]. These cells produce steroid hormones and peptides necessary for folliculogenesis and ovulation. Due to the production of estrogen by these tumors, the frequent symptoms that occur in these patients develop as a result of hyperestrogenism [3]. Histologically, there are two types of GCT, e.g., adult and juvenile. The adult type is much more prevalent, about 95% of all GCT, and occurs in perimenopausal and postmenopausal women most often between 50 and 55 years of age. The second type of GCT is rare and occurs predominantly among young women [1]. These tumors are most commonly detected at an early stage of the disease and have a better prognosis compared to epithelial ovarian tumors [3]. The main treatment is surgical, implying hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and peritoneal biopsy. With about 10% of these tumors occurring in patients in the reproductive period, there is a need for a conservative approach. Determining the stage of the disease is the most important factor in the treatment decision, owing to the fact that the ten-year survival rate is 84-95% for Stage I, 50-60% for Stage II, and 17-33% for Stages III and IV [4]. According to the European Society of Gynaecological Oncology (ESGO) guidelines, the preservation of fertility is safe for tumors that are detected at early stages of IA and IC, where it is necessary to perform a unilateral salpingo-oophorectomy and complete staging [5]. Chemotherapy is administered to treat advanced-stage or high-risk Stage I tumors [4].

Case Report

A 37-year-old patient, G0, P0, was referred to a gynecologist due to irregular bleeding. Hypoechoic tumefaction of the right ovary was diagnosed by ultrasound, 6 cm × 7 cm in diameter, with a proper flow rate (RI 0.44). The patient had suffered from multiple sclerosis since 2001, and was in remission at the time of the discovery of the disease. She went to see a doctor about irregular bleeding, but had no pain or additional complaints. Laboratory, biochemical analysis, and Ca-125 tumor markers were all normal. In July 2016, after preoperative preparation under the conditions of general endotracheal anesthesia, a laparoscopic removal of the described tumor was performed. The uterus, left fallopian tube with ovary, and right fallopian tube were normal. The right ovary was enlarged, with a tumor formation of about 6 cm in diameter. There was no liquid in the abdomen, and there were no visible pathological changes. The tumor was sent for an HP analysis in fragments and lavage was not performed due to the benign pathology that was expected. The surgery and post-operative course went without complications, and a follow-up was scheduled. The results of histopathological findings confirmed an adult-type GCT with medium differentiation, 1/10 mitotic index, and no involvement of lympho-vascular structures.

The patient was presented to the tumor board of Narodni Front Obstetrics and Gynecology Clinic along with her histopathological findings. A staging laparotomy was performed. After the first operation, another surgery was performed, during which swabs were taken paracolically left, right, and subdiaphragmatically, and the lavage was sent.
for cytological analysis. A right salpingo-oophorectomy was performed, together with biopsies of the left ovary and omentum. The histopathological findings showed that the tissue was without any major pH changes, and the cytological analysis of the swabs showed the presence of mesothelioma cell groups. The patient underwent an exploratory endometrial curettage of the uterus, and the histopathological finding was normal. After a follow-up consultation with the Oncology Board, Stage IC1 disease was determined due to surgical dissipation of tumor during the first operation. The decision was made that the patient should undergo three cycles of chemotherapy according to the PEB regimen.

After undergoing chemotherapy, the patient did not show any complications, and after a repeated MRI examination of the pelvis and abdomen, she maintained a regular oncologist regimen.

Nine months after the last cycle of chemotherapy, the patient conceived naturally. She was regularly monitored by ultrasound, and the results of her screening tests were satisfactory. The pregnancy progressed smoothly without complications and resulted in a live birth. She delivered a male child vaginally and at term. The baby weighed 3,550 grams and was 52 cm long, with an Apgar score of 9/10. It was advised that the radicalization of the surgery be performed after the involutive period.

**Discussion**

GCT of the ovary is a very rare neoplasm with good prognosis. In 80-90% of cases, it is detected at Stage I of disease [1]. Due to its low prevalence, the optimal treatment of these tumors has not been determined by randomized studies.

The patient had consulted a gynecologist for irregular bleeding, a common symptom. Due to an increase in estrogen secretion, symptoms that occur are associated with the presence of this type of tumor. In juvenile type GCT, premature puberty occurs in the form of pubic hair growth and vaginal bleeding (5%) [6]. Adult type GCT usually manifests with menorrhagia, intermenstrual bleeding, amenorrhea, or postmenopausal bleeding [7]. Due to hyperestrogenism, the endometrium may also be affected, and endometrial hyperplasia or endometrial cancer may develop. According to published literature, this phenomenon occurs in 20-25% of all cases [8]. For this reason, it is necessary for these patients to undergo exploratory curettage of the uterus, as occurred in the present case.

When dealing with GCT, it is vital to first determine the stage of the disease. The most suitable treatment modality and method can be determined in accordance with the patient’s wishes. Most often the main approach to treatment involves the complete removal of the uterus and ovaries, but conservative treatment can be considered in patients who have a desire to have children, if the disease is detected at an early stage [4]. It is necessary to perform adequate staging of the disease, which implies, in addition to the removal of the diseased ovary, peritoneal flushing, multiple peritoneal biopsies, biopsy of the omentum, and biopsy of any suspicious change.

Prognostic factors include age, tumor stage and size, tumor rupture, mitotic index, and grade. The stage of disease has been found to be the most important prognostic factor. A study showed that only 9% of women with Stage IA had recurrent disease in comparison to 30% in the higher stages [5].

Preservation of fertility is possible in young patients with Stage IA [3]. Studies have shown that there is not much difference in survival between a conservative approach compared to radical surgery (97% vs. 98%, respectively) and where five-year and ten-year survival rates for conservative approach were 97% and 94%, respectively [9].

Patients at the early stage of GCT have a very good prognosis, with survival rates ranging between 89% and 99%, and therefore these patients do not require post-operative treatment. Due to an increased risk of relapse, postoperative chemotherapy should be considered as a treatment option for high-risk patients in the first stage (tumor size greater than 5 cm, Stage IC, high mitotic index, tumor rupture). Several studies have shown that patients with Stage IC ovarian cancer are at a higher risk of relapse and, in this case, additional chemotherapy is recommended, as was administered to the present patient. Naturally, postoperative treatment is recommended for Stages II-IV, but due to the low prevalence of these tumors, there are very few studies suggesting a higher survival rate following the administration of postoperative chemotherapy [10, 11].

In patients with an incidental finding of tumor that have not been adequately staged, it is necessary to perform secondary surgical treatment and restaging [6]. In the case of the present patient, benign pathology was expected thus only an extirpation of the tumor was performed during the first surgery. Subsequently, a complete disease was staged in the second surgery, after which the decision was made for conservative treatment.

After a successful delivery, it is advisable to completely remove the uterus and the remaining ovary, however there are disagreements about this approach [3]. Some studies have shown that complete removal of the uterus can be performed after the relapse of the disease [5]. In the present case, the Oncology Board opted for a radical surgery after the delivery, following the recommendations in some studies [12].

**Conclusion**

For young women with a desire to become pregnant, a conservative approach to treating GCT is acceptable if the tumor is detected at Stages IA and IC. The stage of the disease is the most important prognostic factor, and it is necessary to perform complete surgical staging when making the treatment decision. Chemotherapy in the present patient did not lead to infertility. Further prospective studies are needed for a more precise definition of approaches concerning the removal of the uterus and the remaining ovary after a completed delivery.
Ethics approval and consent to participate

Hereby I confirm that procedures involving experiments of human subjects are done in accord with the ethical standards of the Committee on Human experimentation of the institution in which the experiments were done or in accord with the Helsinki Declaration.

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Conflict of interest

The authors declare no competing interests.

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