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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Successfully completed pregnancy after conservative treatment of nonepithelial ovarian cancer

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SUMMARY

Introduction Granulosa cell tumors are rare neoplasms of the ovary with low malignancy potential and late recurrence. They originate from the granulose of the ovary stromal cells and have the ability to produce estrogen. The main treatment is surgical and implies hysterectomy with bilateral salpingo-oophorectomy, omentectomy, taking peritoneal biopsies, and cytological analysis of the peritoneal washing. When found in young women who have not given birth, a conservative approach can be considered. Fertility sparing surgery is safe only for early FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) stages IA tumors то IC, where it is necessary to make unilateral salpingo-oophorectomy and complete staging.

Case outline We present a case of young woman with granulosa cell tumor who was accidentally discovered, and after an adequate surgery and chemotherapy she gave a birth to a healthy child.

Conclusion Young women who have not given birth and who have been diagnosed with granulosa cell ovarian tumor can be treated conservatively after adequate disease staging and confirmation that the disease is at an early stage.

Keywords: ovarian granulosa cell tumor; fertility sparing surgery in granulosa cell tumors, treatment; prognostic factors; monitoring

INTRODUCTION

Granulosa cell tumors are rare neoplasms and make up 2–5% of all tumors of the ovary. They belong to the subgroups of the sex cord and are most common in this group (70%) [1]. They originate from the granulose of the ovary stromal cells and have the ability to produce estrogens, and thus lead to a clinical manifestation of disease in the form of vaginal bleeding in postmenopausal or prolonged and irregular bleedings in young patients. There are two types: adult, the most frequent, with a frequency of 95%, occurs in menopausal women, and a juvenile type which is less likely to meet with patients under the age of 30 years. [2]

They are distinguished by the gene mutation at the level of fork head transcription factor 2 (FOXL2) located on chromosome 3q23. This gene is responsible for the normal ovarian function, regulates the proliferation of cellular granuloses, the development of follicles, and the synthesis of ovarian hormone. The mutation of FOXL2 gene leads to dysregulation of TGF-β, resulting in abnormal cell proliferation and tumor formation [3]. Mutations on this gene occurs in more than 97% of the adult tumor granuloses and is rarely detected in other cancers [4].

These tumors are most commonly found in the early stage of the disease. They have good prognosis compared to other ovarian tumors, and five-year survival is over 90% [1]. The main treatment is surgical and implies hysterectomy with bilateral salpingo-oophorectomy, omentectomy, taking peritoneal biopsies, and cytological analysis of the peritoneal washing. When they are discovered in patients in the reproductive period, there is a need to preserve fertility. According to the American National Comprehensive Cancer Network (NCCN) of 2017, a conservative approach is justified in patients with Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage IA / IC disease [5].

In the present case, a young patient was diagnosed with a malignant ovarian tumor by accident. Following an adequate disease staging, the patient received adjuvant chemotherapy, and eventually delivered a healthy child.

CASE REPORT

A 27-year-old patient, gravida 0 and para 0 with BMI 17.2 reported to the clinic for surgical treatment of ultrasound diagnostic cysts on the left ovary. The cystic change was 50 × 43 × 20 mm in diameter, with regular Doppler parameters. The patients did not have any discomfort or chronic pain, regular menstrual cycles every 28 days, lasting for five days. In May 2013, a laparoscopic surgery was performed, because there was a cyst with a diameter of five centimeters on the left ovary, partly solid part of the cystic material, the

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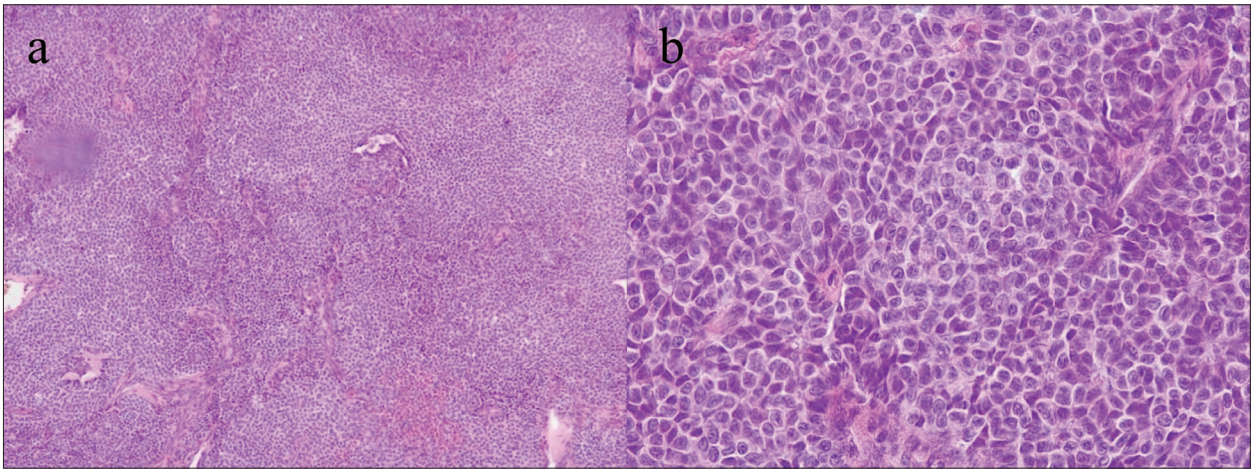

Figure 1. a) The histological features of the tumor: mixed tumor cell population – oval and spindle mononuclear cells with osteoclast-type giant cell (H&E, 100×); b) detail – giant cell soft tissue tumor (H&E, 400×)

uterus, the left ovary, and the fallopian tube were neat and there was no free liquid in the abdomen. A cystectomy of the left ovary was made and the sample was sent in parts to a histopathological examination. The cyst alone had no characteristics indicating malignancy.

Histopathological finding of the cystic ovary involvement indicates that it is a Granulosa cell tumor, an adult type, a medium differentiation, a number of mitosis 3/10, without the involvement of lympho-vascular structures (Figure 1).

Since an inadequate operation was performed for this type of tumor and the stage of the disease was not determined, a month after the first operation, another operation was performed to complete the disease staging according to the FIGO protocol. Lavat, swab paracolic left, right and subdiafragmally were sent to cytological analysis. Left salpingo-oophorectomy, cystectomy and biopsy of the right ovary, and omentum biopsy, were made. Histopathological findings of the left ovary and the fallopian tube are without pathophysiological changes, the biopsy of the right ovary was in order, the removed cyst belonged to the type of paraovarialis cyst and the ometum is also unchanged. The cytological finding was normal without the presence of malignant cells.

Based on this and previous histopathological findings by the multidisciplinary team, the stage of FIGO IC1 disease was identified and it was advised that the patient additionally received three cycles of chemotherapy according to bleomycin, etoposide and cisplatin (BEP) regimen.

After completion of the third cycle of chemotherapy, the repeated magnetic resonance of the small pelvis and abdomen did not show that there were pathological changes and the patient was directed into a regular oncologist regimen.

Three years after the surgery, the patient has undergone in vitro fertilization procedure. An embryo transfer was performed. Pregnancy has passed smoothly without complications. The value of the tumor of the inhibitor B marker that was in order, and was observed the whole time. In July 2017, the patient has undergone a caesarean section, and gave birth to a male child, weighing 3550 grams and 52 cm in length, Apgar score 9/10. Multidisciplinary team advised the patient to undergo a radical surgical procedure of the primary illness after giving birth, which the patient refused.

This case report was approved by the institutional ethics committee, and written consent was obtained from the patient for the publication of this case report and any accompanying images.

DISCUSSION

Tumors of the sexual cord that belong to granulosa cell tumors are rare ovarian neoplasms with low malignant potential and significantly better prognosis compared to much more common tumors of the ovary of epithelial origin. It is significant that in most cases (about 81%) are detected in the early stage of the disease. Their main characteristic is increased estrogen production. This leads to the occurrence of bleeding in women in postmenopausal, or prolonged menstrual or irregular bleeding as well as amenorrhea in young patients, and these are the main symptoms that cause them to visit a doctor [6, 7]. The second common symptom is abdominal pain caused by the size of the tumor, as it is shown that in about 73.5% of cases, the size is over 10 cm, causing pressure on the surrounding organs and distension of the abdomen [8].

An adequate approach in treating patients with this type of tumor involves total hysterectomy with bilateral salpingo-oophorectomy, peritoneal sprains, peritoneal biopsies of the susceptible sites, a biopsy and infracolic omentectomy. Removing the lymph nodes is not recommended unless they are enlarged. Brown et al. [9] in their work involving 262 female patients with a sexual tape tumor showed that none of the 58 patients who underwent lymphadenectomy had any positive metastases in them. A large study involving 1156 patients, of which 572 were subjected to lymphadenectomy in only 3% of cases, the presence of metastases was confirmed. It is further demonstrated that survival is not significant in relation to patients in whom lymphadenectomy has not been conducted [10].

Conservative treatment may be advisable in patients in whom the disease is detected in the early stage of FIGO IA / IC. Preservation of fertility is possible at this stage, as it has been shown that there is no difference in survival in conservative versus radical access, and a total of five years of survival is 97% [11].

Secondary surgical treatment in patients who did not have staging of a disease in the first act is obligatory It implies salpingo-oophorectomy on the side of the tumor, multiple peritoneal biopsies of the suspected sites, blind biopsies, omental biopsy, and cytological analysis of the peritoneal flushing. [12]. The main prognostic factors are the age of a patient, tumor size, mitotic activity, nuclear atypia, but in many studies, it has been found the disease stage is the most reliable prognostic factor [1]. Biopsy of the other ovary is not necessary because this tumor is unilateral in 98% of cases, and on the other hand, we erase the appearance of the progenitor and preserve the ovarian function of the remaining ovarian tissue [13].

It is important to emphasize that due to increased production of estrogen, it can cause changes in endometrium and the appearance of hyperplasia and endometrial carcinoma, and in the case of a conservative approach it is necessary to perform endometrial biopsy to exclude endometrial cancer [14].

The recurrent disease in these tumors is late and amounts to 32–44%. In about 60% of cases, it occurs in the form of local appearance in the small pelvis [1]. Due to this feature, the question arises when it is necessary to perform a complete surgical removal of the uterus and the remaining ovaries, whether after the end of the birth or the occurrence of relapse can be expected. Some authors suggest that it is safe to do with the onset of recurrent disease as some propose radicalization of surgery at the end of birth to reduce the risk of disease spread and increased survival [15].

The use of adjuvant chemotherapy did not improve survival, and its application continues to be controversial, but according to NCCN recommendations it is advised to use adjuvant chemotherapy in a poorly differentiated type, tumor FIGO stage IC, which implies random or spontaneous rupture capsules, as well as in tumors larger than 10 cm [16]. The first line of therapy is combination of BEP, which our patient also received [17].

Studies have shown the high incidence of pregnancy among patient with diagnosed and treated granulose cell tumors. The pregnancy rate is 86.4% and the live-birth rate is 95%.

In managing these data and the fact of a patient's high survival rate when the tumor is detected at an early stage of the disease, we can conclude that a conservative approach to achieve progeny is justified and safe. An adequate staging of disease is the most important approach when making such a decision.

Conflict of interest: None declared.

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Успешно завршена трудноћа после конзервативног третмана неепителног малигног тумора јајника

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САЖЕТАК

Увод Тумори гранулозних ћелија су ретке неоплазме оваријума са ниским малигним потенцијалом и касним рецидивом. Потичу од гранулозних ћелија строме јајника и имају способност да производе естрогене. Главни третман је хируршки и подразумева хистеректомију са билатералном салпингоофоректомијом, оментектомијом, узимањем перитонеалних биопсија и цитолошком анализом перитонеалног испирка.

Када се нађе код младих жена које нису рађале, може се размотрити конзервативни приступ, који је безбедан само за ране стадијуме ФИГО *IA* до *IC*, при чему је неопходно учинити унилатералну салпингоофоректомију и комплетно стадирање болести.

Приказ болесника Представљамо случај младе жене са тумором гранулозних ћелија који је случајно откривен. После адекватне операције и хемиотерапије рођено је здраво дете.

Закључак Младе жене које нису рађале и којима је дијагностикован тумор гранулозних ћелија јајника могу се конзервативно лечити после адекватног стадирања болести и потврде да се болест налази у раној фази.

Кључне речи: тумори гранулозних ћелија јајника; очување фертилитета, лечење; прогностички фактори; праћење