JUVENILE TYPE GRANULOSA CELL TUMOR

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JUVENILNI TIP GRANULOZA ĆELIJSKOG TUMORA

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Received / Primljen: 12. 12. 2016. Accepted / Prihvaćen: 04. 05. 2017.

ABSTRACT

Granulosa cell tumor is a type of neoplasm, which represents 2-5% of all ovarian cancers. About 5% of these tumors are juvenile-type and usually occur to girls before puberty and to women younger than thirty years of age. There are signs premature puberty or premature emergence of secondary sexual characteristics with irregular vaginal bleeding that occur to these kind of patients. To the rare cases, like this, the occurrence of granulosa cell tumors can cause the appearance of hyperandrogenism with high levels of plasma testosterone, leading to virilization which happened to this female patient. We will present the female patient who was 35 years old and which was originally hospitalized to the Clinic for Haematology Clinical Center Kragujevac, because of extreme fatigue accompanied by dizziness. During diagnostics the patient underwent to the complete gynecological examination. After gynecological examinations and necessary diagnostic procedures, it was decided continuing the treatment at the Clinic of Gynecology and Obstetrics Clinical Center Kragujevac, where she underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy for suspected uterine neoplasm. Histopathological analysis of the obtained material confirmed the presence of follicular cysts of both ovaries and juvenile type granulosa cell tumor on the right ovary; the uterus was enlarged with multiple fibroid tumors. Granulosa cell tumor should be suspected in the cases of girls and young females if there is present an ovarian cyst paired with signs of preterm puberty or hyperestrogenism. In this case, the presence of granulosa cell tumor was masked by signs of hyperandrogenism, which is not so typical, as well as the presence of uterine fibroids who have actually been the main cause for surgical treatment.

Keywords: *juvenile-type granulosa cell tumor, hyperandrogenism, virilization.*

SAŽETAK

Tumor granuloza ćelijskog tipa je neoplazma koja predstavlja 2-5% svih karcinoma ovarijuma.Juvenilni tip čini 5% ovih tumora i obično se javlja kod devojčica pre puberteta i kod žena mlađih od trideset godina.Kod ovakvih pacijentkinja javljaju se znaci preveremenog puberteta odnosno prevremena pojava sekundarnih polnih karakteristika uz iregularna vaginalna krvarenja.U veoma retkim slučajevima pojava granuloza ćelijskog tumora može usloviti pojavu hiperandrogenizma sa visokim vrednostima testosterona u plazmi,koji dovode do virilizacije kao kod naše pacijentkinje.Ovde je prezentovan slučaj pacijentkinje koja ima 35 godina i koja je inicijalno primljena na Kliniku za Hematologiju KC Kragujevac,zbog izrazite malaksalosti praćene vrtoglavicom. U toku dijagnostike konsultovan je ginekolog.Nakon obavljenog ginekološkog pregleda i neophodnih dijagnostičkih procedura, odlučeno je da se lečenje nastavi na Klinici za Ginekologiju i Akušerstvo KC Kragujevac,gde je urađena totalna abdominalna histerektomija sa obostranom adneksektomijom zbog sumnje na neoplazmu uterusa.Histopatološka analiza dobijenog materijala je potvrdila obostrano prisustvo mioma u uvecanoj materici,folikularnih cista jajnika kao i juvenilni tip granuloza ćelijskog tumora na desnom jajniku. Granuloza ćelijski tumor se javlja kod devojčica i mlađih adolescentkinja uglavnom sa znacima hiperestrogenizma i prevremenog puberteta. U prezentovanom slučaju prisustvo tumora je bilo zamaskirano izraženom maskulinizacijom koja nije toliko karakteristična, kao i prisustvom mioma uterusa koji su u stvari bili glavni razlog operativnog lečenja.

Ključne reči:*juvenilni tip granuloza ćelijskog tumora,hiperandrogenizam,virilizacija.*

ABBREVIATIONS

HE4- human epididymis protein 4
MRI-Magnetic Resonance Imaging
DHT- dihydrotestosterone

sciendo
UDK: 618.11-006-053.2 / Ser J Exp Clin Res 2018; 19 (4): 389-392
DOI: 10.1515/SJECR-2017-0016

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INTRODUCTION

Ovarian cancers represent fourth most common malignancy in women, after breast, lung and colorectal cancer. The incidence of their appearance ranges from 2-13 per 100,000 women; it affects women of all ages, although more than 75% of affected women are over 45 years old.[1] Ovarian cancers are divided into three histological groups:

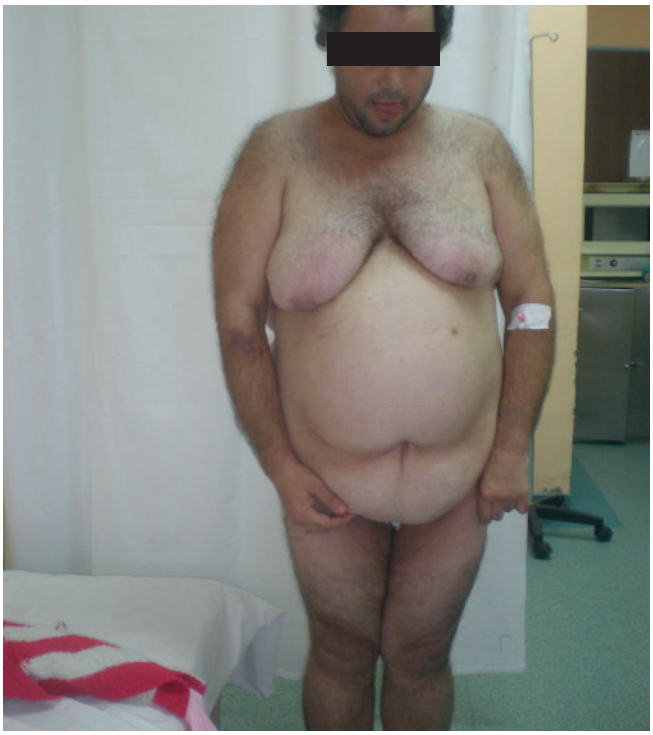
- Ovarian cancers deriving from germline cells which affects mainly young women
- Ovarian cancers of the epithelial origin typical for the elderly women
- Ovarian cancers of the stromal origin which can occur in all age groups

Granulosa cell tumor represents 2-5% of all ovarian cancers.[2,3] It originates from the granulosa cells, hormonally active ovarian stromal component, primarily responsible for the secretion of estradiol; thus, the main characteristic of these tumors is hyper production of estrogen.[4,5] Based on the histopathological and clinical characteristics granulosa cell tumor is divided into juvenile and adult type. Juvenile type of the granulosa cell tumor usually occurs to the young girls or women before thirty years of age. The presence of the juvenile form of the tumor can lead to premature puberty, or premature emergence of secondary sexual characteristics with irregular vaginal bleeding.[6] Adult form of the granulosa cell tumor can also lead to irregular vaginal bleeding but with connection to endometrial or breast carcinoma.[7] In very rare cases, granulosa cell tumor can cause hyperandrogenism, with high level of plasma testosterone which results in overt virilization of the patient.[8,9,10] We represent the case of a patient with juvenile form of granulosa cell tumor , with extreme virilization which is seen in the clinical presentation of the illness.

CASE REPORT

Thirty-five years old patient, with visible hirsutism and severe obesity, was hospitalized at the Clinic of Hematology, Clinical Center in Kragujevac, because of extreme fatigue, accompanied by vertigo and dizziness. According to the medical history, abovementioned ailments occurred a few months ago and got worse in the last couple of weeks. Furthermore, medical history showed that the patient had a menarche at the age of eighteen, and since then she had frequent, heavy and prolonged menstrual cycles. The routine blood test, taken upon submission, showed severe secondary anemia (Er 1.97, Hgb 36), while the immunochemical analysis of the concentration of the plasma sex hormones, as well as other steroids, showed only high levels of testosterone (198 ng / ml). Because of the severe hirsutism and virilization, a karyotype from the peripheral white blood cells has been done and it showed a female sex (46 XX). Afterwards, the patient underwent to the gynecological examinations, which showed hypertrophy of the clitoris with diminished vaginal opening. Considering that the patient was a virgin, gynecological exam had to be done via rectal route, and it showed uterine myomatosis with enlarged uterus, about twenty centimeters in diameter. Adnexal examination showed that both sides were physiologically available, insensitive on palpation. Following ultrasonography of the pelvis showed the enlarged uterus, 180x155x125 mm in diameter, with numerous fibroid nodes of which the largest was 6x5 cm in diameter. Dimensions of the right ovary were 45x25mm, while left was 35x20mm in diameter, with no pathological findings. Values of the tumor markers CA 125 (0-35 / ml) and HE4 (below 73 pmol/L) were within normal range. Radiography of the abdomen and thorax showed no presence of pathological changes. The MRI findings matched the ones obtained by ultrasound; it also showed enlarged uterus 185x157x125mm diameter, with numerous intramural fibroids. Both ovaries were of normal morphology, with dimensions 43x25mm for the right, and 33x19mm for the left. MRI examination also showed the absence of enlarged lymphatic nodes in the parametrical or near pelvic main blood vessels. After all examinations, a consilium's decision has been to carry on the patient treatment on Clinic of Gynecology and Obstetrics, Clinical Centre Kragujevac. Upon adequate preparation, the patient underwent operative treatment; a classic abdominal hysterectomy with bilateral salpingo-oophorectomy was done, on suspicion of uterine neoplasm. Surgery and postoperative course passed without complications, and the patient was discharged from the hospital in due course, with corresponding hormone replacement therapy. Immunochemical analysis of the concentration of the plasma sex hormones which has been done a week after surgery, were in the domain of reference values (testosterone 0.6 ng / ml).

Histopathological analysis of the obtained material was performed at the Department of Pathology of the Clinical Center in Kragujevac. Uterus weight was 1880 grams, and it diameter was 180x150x125mm, while lower part was filled with blood cloths. The tissue cross section demonstrated diffusely thickened walls composed of swirling arranged muscle cells, with proliferation of the endometrium. The right ovary was 47x34mm in diameter, while cross section showed cystic amended stroma, with cysts ranging in diameter from 4 to 8 mm, filled with clear content; and one solitary brown node 30mm in diameter. Left ovary was 48x38mm in diameter, with cross section also showing cystic changes, with cysts ranging in diameter from 3 to 9 mm, all filled with clear content. The microscopic analysis of the uterine tissue confirmed the presence of multiple fibroid tumors, while microscopically ovaries were interleaved with mutual follicular cysts, with juvenile type of granulosa cell tumor in the right ovary.



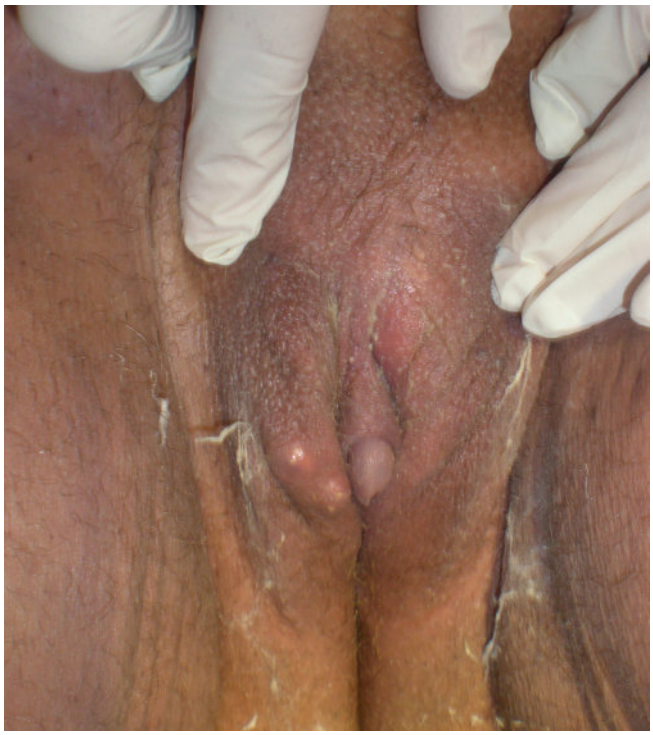
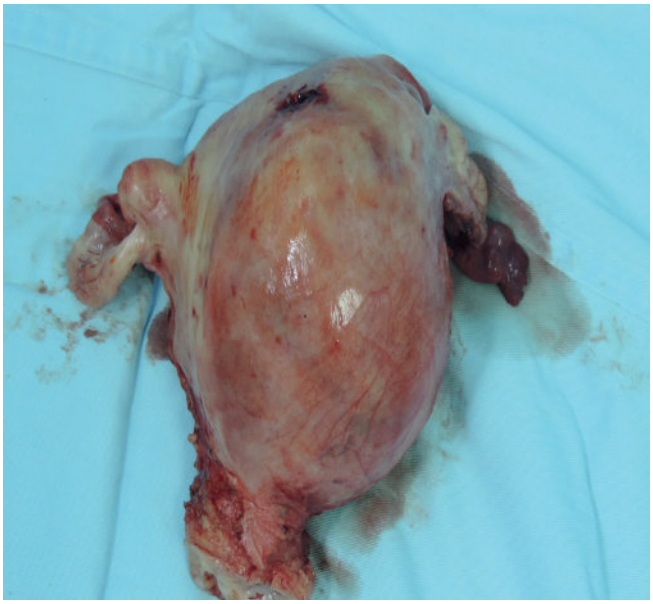


Figure 1. Severe obesity with visible hirsutism . Clitoromegaly.

DISCUSSION

Ovarian tumors are rare occurrence in girls and younger women. Granulosa cell tumor make up only 2% of all malignancies of the ovary, while juvenile type granulosa cell tumor constitutes 5% of juvenile ovarian cancers and is usually manifested in the first thirty years of life.[11,12] The granulosa cell tumors are associated with the occurrence of premature puberty, menstrual cycle disorder and in the rare cases it causes virilization. Masculinisation and virilization of the patient can be explained by the insufficiency of the enzyme aromatase in the granulosa cells of the ovarial stroma, and the overproduction of androgens instead estrogens.[8,9,10] In the rare and the most extreme cases, hyperadrogenism can lead to the appearance of hirsutism, accelerated growth and clitoromegaly, to a such degree that it raises the suspicion of genetically determined sex, as it was shown in this case report. The effect of the androgen hyper production is increased by conversion of testosterone to much more



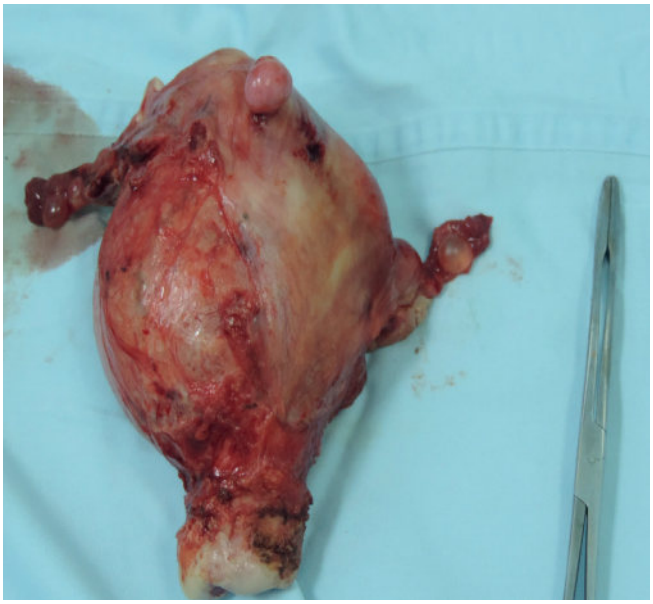


Figure 2. Multiple fibroid tumors of uterus.Mutual folicular cysts both ovary.

potent dihydrotestosterone (DHT), in the androgen-dependent tissues, by the enzyme 5-alpha-reductase.[13] Apart from converting testosterone into a more potent form, enzyme 5-alpha-reductase increases the sensitivity of cell receptors for androgens, which may explain severe masculinisation in our patient (figure 1). The granulosa cell tumors are often unilateral, solid, well-differentiated and have a small malignant potential.[14] The diagnosis of granulosa cell tumors is based on the clinical presentation of the illness, and additional diagnostic procedures such as ultrasonography, magnetic resonance imaging or computed tomography. The differential diagnosis should exclude diseases of the other parts of the endocrine system, especially the pituitary and adrenal glands.[15,16] The treatment of the juvenile type of granulosa cell tumor is exclusively surgical, by ophorectomy or adnexectomy, after which the symptoms of masculinisation can spontaneously disappear.

CONCLUSION

Granulosa cell tumor should be suspected in girls and young females cases if there is present an ovarian cyst paired with signs of preterm puberty or hyperestrogenism. In this case, the presence of granulosa cell tumor was masked by signs of hyperandrogenism which is not so typical, as well as the presence of uterine fibroids who have actually been the main cause for surgical treatment.

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