



Case report

JUVENILE GRANULOSA CELL TUMOR IN A 5 YEARS-OLD BULGARIAN GIRL PRESENTING WITH PRECOCIOUS PUBERTY: A CASE REPORT

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ABSTRACT:

Ovarian tumors in children before puberty are rare and usually non-malignant. Granulosa cell tumors are rare sex cord-stromal tumors, accounting for 5% of all ovarian tumors and occur mainly in premenarchal girls and in women younger than 30 years.

The diagnosis is based on the presence of precocious puberty, advanced bone age, palpable abdominal mass, nonspecific abdominal pain and abdominal swelling, vaginal discharge. In adolescent, it manifests with signs of menstrual irregularity and virilization.

This is a case report of a 5-year-old Bulgarian patient with clinical and paraclinical findings of peripheral precocious puberty who underwent unilateral salpingo-oophorectomy after US and MRI was performed. From the performed imaging studies, Juvenile granulosa cell tumors was suspected. Histological findings confirmed the primary diagnosis – Granulosa cell tumor of juvenile type and TMN staging was: pT1a. It was decided not to perform adjuvant chemotherapy in view of the stage of the tumor process according to existing algorithms and the decision of the oncology committee.

Generally, the prognosis is good. The most important prognostic factor associated with a higher risk of relapse is the stage of disease. Prolonged surveillance is essential in the described case because the disease tends to recur years after the initial diagnosis.

Keywords: Juvenile ovarian granulosa cell tumors (JOGCT), Pediatric, Precocious puberty,

INTRODUCTION:

Ovarian tumors in children before puberty are rare and usually non-malignant. According to the Surveillance, Epidemiology, and End Results (SEER) registry, the age-adjusted incidence of malignant ovarian tumors is 0.102 per 100,000 in less than 9 years of age as compared to 1.072 per 100,000 in those between 10 and 19 years. In all age groups, the usual pathology is germ cell tumor. Among the malignant sex cord-stromal tumors, the most common type is granulosa cell tumors. As they arise from sex cords and stroma, they usually contain both a follicular and stromal component. The granulosa cells determine their malignancy [1].

Ovarian granulosa cell tumors are classified into two groups based on their clinico-pathological characteristics; juvenile (JGCOT) and adult type (AGCOT). JGCOT comprises 5% of all granulosa cell neoplasms. Generally, it occurs in premenarchal girls or young women [2]. These tumors are unilateral in the majority of cases. They are usually presented as a large mass with a smooth surface and solid and/or cystic components. The clinical presentation of JGCTs can include symptoms such: precocious puberty, early breast development, increased pubic hair, advanced bone age, palpable abdominal mass, nonspecific abdominal pain and abdominal swelling, vaginal discharge. In adolescent, it manifests with signs of menstrual irregularity and virilization [3].

Regarding the diagnostic process, the existing guidelines suggest using both imaging tests (at least ultrasound of the abdomen and pelvis) and the measurement of a basic panel of serum tumor markers, while there is debate around the necessity of MRI and the diagnostic value of PET scan. There is a consensus among guidelines about the significant role of molecular biology and immunohistochemistry in confirming the diagnosis.

In order to ensure optimal management and due to the rarity of these cases, paediatric and adolescent patients with suspected ovarian malignancies should be referred to a specialized center with a multidisciplinary team composed of trained gynaecological and paediatric

oncologists with experience in such cases. Abdominal and pelvic ultrasound is the initial imaging of choice when investigating ovarian tumours in young patients, and it should be performed. The endometrial thickness should be evaluated, especially when SCSTs are suspected. Additional imaging is required - ESGO-SIOPE guidelines suggest that thoracic computed tomography (CT) scan and abdomino-pelvic magnetic resonance imaging (MRI) are necessary and useful in evaluating bilateral ovarian masses and choosing the most appropriate surgical approach without exposing the patient to radiation. On the other hand, an abdomino-pelvic computed tomography (CT) scan and chest X-ray are suggested by ESMO guidelines as additional preoperative imaging tests, while guidelines by EXPeRT/PARTNER 2021 recommend chest X-rays for the identification of distant metastases, with the alternative of a low-dose chest CT scan.

There is a consensus among all guidelines that serum tumour markers, especially β -human chorionic gonadotropin (β -hCG), alpha-fetoprotein (AFP), lactate dehydrogenase (LDH) and cancer antigen 125 (CA125), should be measured in all ovarian masses with suspicious features. A hormonal profile, including estrogen, testosterone, dehydroepiandrosterone, dehydroepiandrosterone sulfate, luteinizing hormone and follicle stimulating hormone levels, is also essential when signs of hormonal production and precocious puberty are identified. Other biomarkers can also be useful; anti-Mullerian hormone (AMH) and inhibin B may indicate the presence of granulosa cell tumours. Preoperative measurements of tumour markers can provide both diagnostic and prognostic information. In case they are preoperatively elevated, repeated measurements should be performed postoperatively and before the start of adjuvant treatment (for patients receiving adjuvant chemotherapy, new measurements should be obtained before each cycle of treatment).

Complete surgical staging is imperative in patients with SCSTs, including peritoneal fluid sampling or peritoneal washings, unilateral adnexectomy, examination of the contralateral ovary, large omental biopsy or infracolic omentectomy, endometrial curettage for older patients, random blind peritoneal sampling and resection of any suspicious lesions. Total hysterectomy as part of initial surgery should only be performed in patients with stage II+ disease, while omentectomy is recommended only in cases of adhesions to the omentum and not as a routine procedure. Systematic lymphadenectomy is not recommended, but the excision of lymph nodes with suspicious preoperative or intraoperative findings is encouraged. Patients with confirmed Stage IA disease should be treated only with surgery. Tumours staged higher than IA (or higher than IB) may require chemotherapy, which usually consists of three or four cycles of cisplatin-based regimens, mainly BEP, while carboplatin-paclitaxel is also an

acceptable option. Juvenile granulosa cell tumors, patients with stage IA-IC1 disease and complete surgical resection may avoid chemotherapy, which is otherwise required for stages IC2-IC3 (and potentially for IC1, according to ESMO guidelines [4, 5, 6].

Generally, the prognosis is good. The most important prognostic factor associated with a higher risk of relapse is the stage of disease. Although the overall response rate (RR) is high, the impact on disease-free or overall survival is unknown. Due to their tendency to recur years after the initial diagnosis, prolonged surveillance is essential [7, 8].

MATERIALS AND METHODS:

The patient was evaluated using a diagnostic protocol that included clinical, hormonal, sonographic, MRI, and immunohistochemical examinations. The team counselled the parents regarding the treatment modality. Unilateral salpingo-oophorectomy was performed, as well as omentectomy and peritoneal wash. The International Federation of Gynecology and Obstetrics (FIGO) classification was used for staging.

CASE PRESENTATION:

Basic information

A 5-year-old female presented with a 2-month history of precocious puberty – sudden and rapid breast development of Tanner stage III and profuse vaginal discharge, without any other subjective complaints. On physical examination, the girl was within the 80th centile of height and weight for her age - 122 cm height and 23 kg weight. The results of her blood test were – normal blood count, without any deviation. LH <0.30 IU/L (up to 0.20 UI/L), FSH <0.30 IU/L (1.00-4.20 UI/L), estradiol 153.00pmol/L (up to 55.00 pmol/L), testosterone <0.09 nmol/L (0.10-1.12 nmol/L), prolactin 193.mIU/L (33.00 - 280.00mIU/L). There were signs of peripheral precocious puberty with a normal range of serum level of gonadotropins for her chronological age and elevated serum levels of estradiol.

A transabdominal ultrasound examination was performed, and the result was - a heteroechoogenic mass with the presence of solid and cystic components with dimensions - 55.9/46.85 mm, which evolved from the right ovary (Fig. 1). Color Doppler revealed low resistance vascularity. The uterus had a pubertal configuration, with a large fundus and a thickened endometrial stripe of 2 mm. In the left ovary, no pathological findings were found, except discreet enlargement size compared to the child's age and the presence of follicles of different calibers. Tumor markers were investigated – CEA- 0.648 μ g/L (up to 5.500 μ g/L), AFP- 1.070 U/ml (up to 9.960 U/ml), ROMA - 16.11 % (up to 11.40 %), HE 4 - 73.10 pmol/L (up to 70 pmol/L), Ca-125 - 8.850 U/ml (up to 35.00 U/ml).

Fig. 1. Transabdominal ultrasound examination of heteroechogenic mass with the presence of solid and cystic components with dimensions – 55.90/46.85 mm, which evolved from the right ovary.

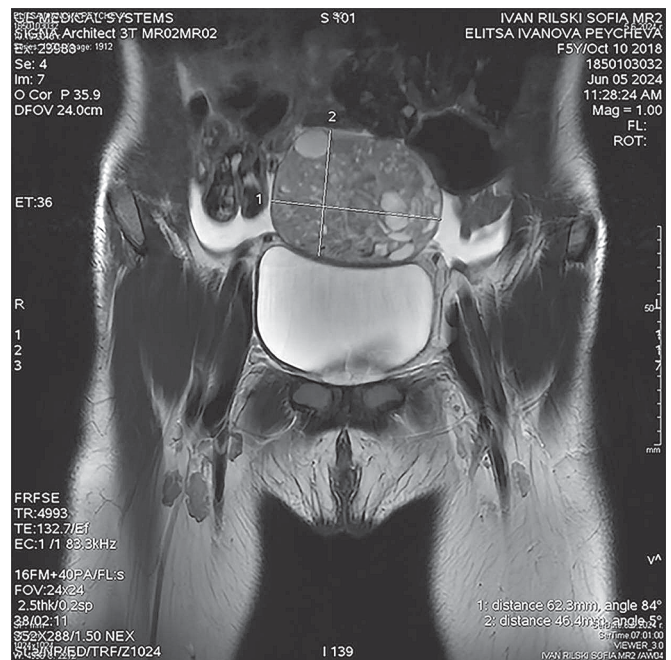


Multiparametric magnetic resonance imaging of a small pelvis was performed - native and after administration of contrast, and the result was MR evidence of a small amount of ascites in the pelvis. The bladder is well-filled, has standard wall thickness, and has no pathological lesions in its lumen. The uterus, in an indifferent position, was not enlarged. The left ovary was not enlarged, with sagittal dimensions: 22.1/10.4 mm and the presence of cysts of various sizes in its structure. In the region of the right ovary, a well-defined, irregular shape with lobulated contours and a heterogeneous structure, with the presence of solid and cystic components was visualized. The lesion had axial dimensions: 62/44 mm and coronal dimensions: 62/46 mm, with a zone of restriction of the diffusion of water molecules (Fig. 2). After the intravenous introduction of contrast material, it increased its signal intensity inhomogeneously, at the expense of its solid component. Rectum - with normal wall thickness, without pathological lesions in its lumen. Perirectal adipose tissue - intact.

There was no MRI evidence of pathologically enlarged lymph nodes from the pelvic circuits and bilaterally inguinal. No pathological lesions were visualized in the structure of the pelvic bones covered by the scan.

Conclusion: An MRI image of the described lesion

Fig. 2. Multiparametric magnetic resonance imaging of the region of the right ovary.



in the region of the right ovary in clinical correlation could be associated with a juvenile granulosa cell tumor of the ovary. A germ cell tumor could be considered in the differential diagnosis.

Treatment:

We took a decision to perform a fertility-sparing surgery - right salpingo-oophorectomy without breach of capsule. Surgical staging was FIGO Stage 1A. The access was median laparotomy with the goal of complete ablasticity and accurate staging. During the surgery, a peritoneal washing was done before salpingo-oophorectomy, and an omentectomy was accomplished to stage the process. After removal of the right adnexus, an express histological evaluation was done with the result: a tumor formation 7x6.5x5 cm, whitish on section, solid cystic. A sex-cord tumor (Fig.3). The final histological examination showed a juvenile-type granulosa cell tumor. From the omentum - mature adipose tissue with hyperemic vessels and focal mesothelial proliferation. From abdominal wash: hypocellular cytogram with the presence of complex mesothelial cells.

Fig. 3. Tumor from the right ovary, intact capsule with smooth surface; oval shape, 7x6,5x5 cm in size; cut section - solid and cystic fields, yellowish in color with a hemorrhage; uterine tube – 7 cm.

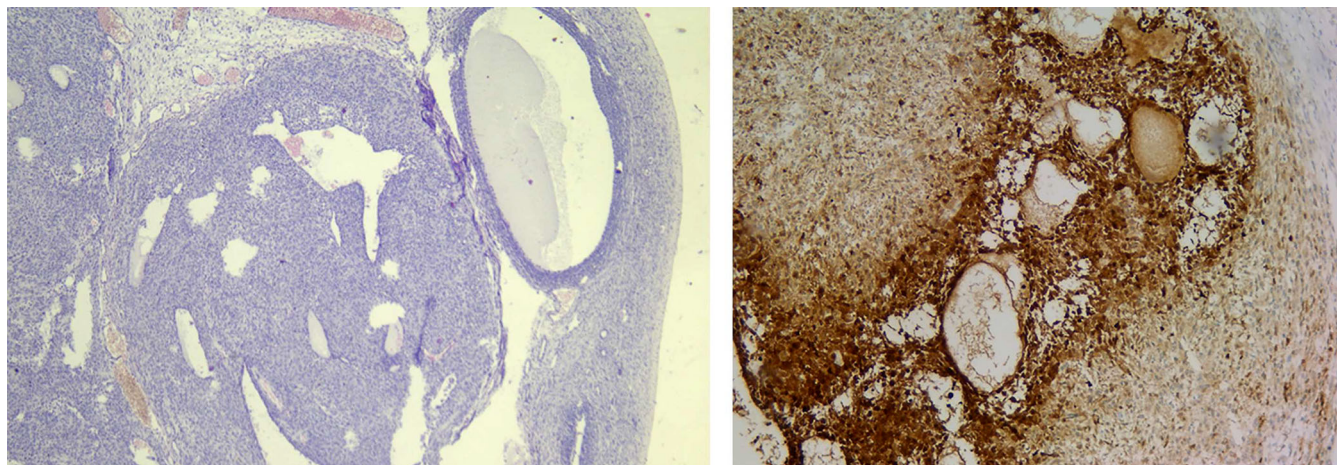


An immunohistochemical examination was performed, and the results were: Calretinin—positive reaction, Inhibin—focally positive reaction, and CD 56—positive reaction. The conclusion of the conducted immunohisto-

chemical examination was: Granulosa-cell tumor of juvenile type (Fig. 4).

TMN staging was: pT1a; morphological code: 8622/1

Fig. 4. Histopathology: ovary parenchyma and adjusted tumor composed of monomorphic, polygonal cells with multinodular, predominantly solid growth, focally organized in follicles filled with basophilic fluid; tumor cell with amphiphilic cytoplasm, vesicular nuclei, rarely nuclear grooves; mitotic figures 8/10HPF; edematous stroma. IHC: inhibin – focally positive, calretinin – positive reaction, CD56 – positive.



Prognosis and follow-up:

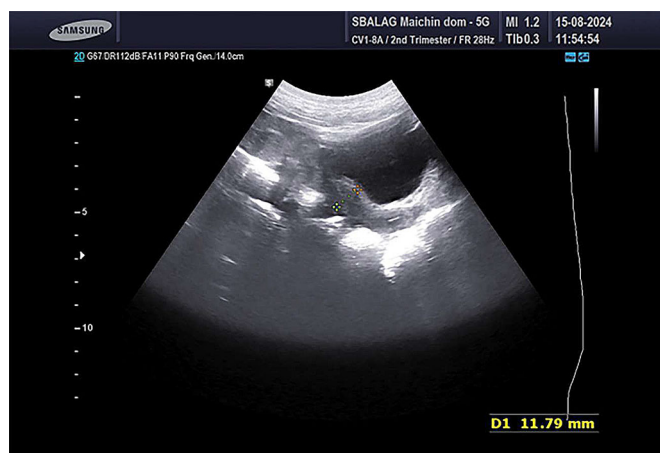
The case was presented to an oncology committee, which decided on dispensary surveillance, including: Examination of tumor markers and ultrasound evaluation once every three months for the first three years and once every six months until the fifth year, as well as conducting an MRI with the contrast of the whole body once a year.

It was decided not to perform adjuvant chemotherapy in view of the stage of the tumor process.

At the first examination three months after the surgery, the ultrasound findings showed a significant reduction in the size of the uterine body - anterior-posterior size 11,79 mm and reduced volume of the left ovary – 25.9/

15.8 mm (Fig. 5). The endometrium showed no signs of estrogenic influence. Tumor markers were negative - Inhibin B 5.88 pg/ml (40.00-200.00 pg/ml), CEA 0.890 µg/l (up to 5.500 µg/l), AFP 2.10 U/ml (up to 9.96 U/ml), HE 4 51.70 pmol/l (up to 70 pmol/l), CEA 125 8.570 U/ml (up to 35.00 U/ml). Cerum estradiol levels normalized and fell to <18.40 pmol/l. LH <0.30 IU/L, FSH 1.23 IU/L (1.00-4.20 IU/L), Testosterone <0.09 nmol/L (0.10 – 1.12 nmol/L). Her post-operative course was uneventful, and her breast returned to the prepubescent stage. The vaginal discharge stops a few weeks after the surgery.

Fig. 5. Transabdominal ultrasound examination three months after the surgery - significant reduction in the size of the uterine body - anterior-posterior size 11,79 mm and the endometrium showed no signs of estrogenic influence.



DISCUSSION AND CONCLUSION:

Granulosa cell tumors are hormonally active neoplasms derived from sex cord stromal tumors, which originate from mesenchymal cells and are totipotent. These neoplasms are uncommon in children and adolescents. About 90% are diagnosed in early-stage FIGO I with a favorable prognosis [1]. Ovarian granulosa cell tumors are classified into two groups based on their clinico-pathological characteristics; juvenile (JGCOT) and adult type (AGCOT). JGCOT comprises 5% of all granulosa cell neoplasms [2]. In the University Obstetrics and Gynecology Hospital “Maichin dom” Sofia, Bulgaria, that was the first case of JGCT in the premenarchal patient in the last 20 years.

JGCT usually present with symptoms and signs of isosexual precocious puberty, including breast development, pubic and axillary hair growth and vaginal bleeding in prepubertal girls. The classical triad is described as a palpable adnexal mass, raised serum estradiol, and absent or decreased gonadotropins [1,3]. Our case had a presentation of precocious puberty with rapid breast development Turner stage III and vaginal discharge, and her laboratory studies were pointing towards peripheral precocious puberty with elevated serum levels of estradiol and normal gonadotropins.

Abdominal and pelvic ultrasound is the initial imaging of choice when investigating ovarian tumours in young patients, and the endometrial thickness should be evaluated, especially when SCSTs are suspected. A transabdominal ultrasound examination was performed and the result was - heteroehogenic mass with the presence of solid and cystic components with dimensions - 64/52 mm, which evolved from the right ovary. Color Doppler revealed low resistance vascularity. The uterus had a puber-

tal configuration, with a large fundus and a thickened endometrial stripe of 2 mm.

Additional imaging is required - ESGO-SIOPE guidelines suggest that thoracic computed tomography (CT) scan and abdomino-pelvic magnetic resonance imaging (MRI) are necessary and useful in choosing the most appropriate surgical approach without exposing the patient to radiation. In our case, Multiparametric magnetic resonance imaging of a small pelvis was performed - native and after administration of contrast and the result was an MRI image of the lesion in the right ovary could be associated with a juvenile granulosa cell tumor. [4].

There is a consensus among all guidelines that serum tumour markers, especially β -human chorionic gonadotropin (β -hCG), alpha-fetoprotein (AFP), lactate dehydrogenase (LDH) and cancer antigen 125 (CA125), should be measured in all ovarian masses with suspicious features. Other biomarkers can also be useful; anti-Mullerian hormone (AMH) and inhibin B may indicate the presence of granulosa cell. Preoperative measurements of tumour markers can provide both diagnostic and prognostic information. In case they are preoperatively elevated, repeated measurements should be performed postoperatively and before the start of adjuvant treatment (for patients receiving adjuvant chemotherapy, new measurements should be obtained before each cycle of treatment. In our case, tumor markers that were investigated – CEA, AFP, ROMA - 16.11 %, HE 4 - 73.10 pmol/L, Ca-125, only ROMA index and HE4 were above the upper limit of reference values, which are not usually elevated in this type of tumor. Unfortunately, Inhibin A/B and AMH were not included in the panel of tumor markers [1, 4].

Complete surgical staging is imperative in patients with SCSTs, including peritoneal fluid sampling or peritoneal washings, unilateral adnexectomy, examination of the contralateral ovary, large omental biopsy or infracolic omentectomy, endometrial curettage for older patients, random blind peritoneal sampling and resection of any suspicious lesions. We took a decision to do the right salpingo-oophorectomy as a fertility-sparing surgery. The access was median laparotomy with the goal of complete ablasticity and accurate staging. During the surgery, a peritoneal washing was done before salpingo-oophorectomy, and an omentectomy was accomplished to stage the process. During the surgery, the condition of all abdominal organs, peritoneum and contralateral ovary was assessed. No suspicious lesions were found. The surgical staging was FIGO Stage 1A [1, 3, 4].

There is a consensus among guidelines about the significant role of molecular biology and immunohistochemistry in confirming the diagnosis. An immunohistochemical examination was performed after the salpingo-oophorectomy, and the result was: Calretinin, Inhibin, CD 56 - positive reaction, which confirmed the diagnosis:

Granulosa-cell tumor of juvenile type and TMN staging was: pT1a [4]. Our case was presented to an oncology committee, and the conclusion according to the tumor stage was dispensary surveillance with an evaluation of tumor markers and ultrasound examination once every three months for the first three years and once every six months until the fifth year, as well as conducting an MRI with the contrast of the whole body once a year. It was decided not to perform adjuvant chemotherapy. According to guidelines given by ESMO 2018, ESGO-SIOPE 2020, Centres Experts TRMG 2022, EXPeRT/PARTNER

2021, patients with confirmed Stage IA disease should be treated only with surgery [4, 5, 6].

Generally, the prognosis is good. The most important prognostic factor associated with a higher risk of relapse is the stage of disease. The tendency to recur years after the initial diagnosis, prolonged surveillance is essential like in the described case – five years [7, 8]. The postoperative course of our patient was uneventful, and her breast development returned to the premenarchal stage. The vaginal discharge stops a few weeks after the surgery.

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