J Surg Med. 2020;4(2):167-169.
DOI: 10.28982/josam.636136

Case report
Olgu sunumu

Journal of Surgery and Medicine
e-ISSN: 2602-2079

A rare cause of precocious puberty: Juvenile granulosa cell tumor

Puberte prekoksun nadir bir nedeni: Juvenil granüloza hücreli tümör

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Informed Consent: The authors stated that the written consent was obtained from the parents' of the patient presented with images in the study.
Hasta Onamı: Yazar çalışmada görüntüleri sunulan hastanın ebeveynlerinden yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 2/29/2020
Yayın Tarihi: 29.02.2020

Abstract

Ovarian sex cord-stromal tumors, including granulosa cell tumors are rare, especially in children. They are classified into juvenile and adult types. Juvenile granulosa cell tumors (JGCT) comprise 5% of all granulosa cell tumors. Precocious pseudo-puberty is a common presentation of these tumors, associated with hormonal changes. We report a rare case of JGCT of the ovary in a 4-year-old girl who presented with breast enlargement and alveolar pigmentation for two months. At her examination she had also an abdominal mass. Based on imagining features and laboratory findings, the diagnosis of the mass was unclear. After surgery, histopathological examination revealed JGCT of the left ovary. Although in most of girls with precocious puberty, the etiology is idiopathic, important causes, such as ovarian tumors like JGCTs must be considered.

Keywords: Juvenile granulosa cell tumor, Ovary, Puberty

Öz

Granüloza hücreli tümörleri içeren over seks kord stromal tümörleri, özellikle çocuklarda nadir görülen tümörlerdir. Juvenil ve yetişkin tip olarak iki gruba ayrılırlar. Juvenil granüloza hücreli tümörler (JGHT) tüm granüloza hücreli tümörlerin %5'ini içerir. Yalancı puberte prekoks, hormonal değişiklikler ile ilişkili bu tümörlerin en sık görülen bulgusudur. Biz burada 2 aydır meme büyümesi ve alveoler pigmentasyon şikayeti ile başvuran, 4 yaşındaki bir kız çocuğunda görülen nadir bir JGHT olgusunu bildirdik. Muayenesinde abdominal kitlesi de mevcuttu. Görüntüleme ve laboratuvar bulguları ile kitlenin tanısı belirsizdi. Operasyon sonrası histopatolojik tanı sol overin JGHT' ü olarak konuldu. Puberte prekoksu olan kızların çoğunda etyoloji idiyopatik olsa da JGHT de içeren bazı over tümörleri gibi önemli nedenler göz önünde bulundurulmalıdır.

Anahtar kelimeler: Juvenil granüloza hücreli tümör, Over, Puberte

Introduction

Granulosa cell tumors are the most common malignant sex-cord stromal tumors, and they are classified into juvenile and adult types [1]. Juvenile types constitute only 5% of the granulosa cell tumors [1]. JGCTs most commonly occur in peripubertal girls and in women younger than 30 years of age, at the mean age of 13 years [2]. Precocious pseudo-puberty, a common presentation of these tumors, is related to hormonal changes [3]. We herein present a rare case of JGCT in a 4-year-old girl with isosexual precocity as premature thelarche.

How to cite / Atıf için: Özkan A, Kor Y, Koç AS, Özçelik Z, Aydın EB. A rare cause of precocious puberty: Juvenile granulosa cell tumor. J Surg Med. 2020;4(2):167-169.

Case presentation

A girl, at the age of 4 years and 4 months, with no significant past medical history, presented with breast enlargement and alveolar pigmentation for the last 2 months (Figure 1). On physical examination, her pubertal stage was Tanner 3 for breast development and Tanner 1 for pubic and axillary hair growth. Anthropometric evaluation revealed 110 cm height (within the 90th percentile), 22 kg weight (within the 90th to 97th percentile), and a body mass index of 18.2 kg/m^2. She had no headaches or visual complaints. Her bone age was advanced (6 years old). She had a large abdominal mass. She was referred to the Pediatric Endocrinology Clinic in our medical center. Her serum hormonal profile was consistent with peripheral precocious puberty: Estradiol 65 pg/ml; follicle-stimulating hormone (FSH):0.23 mIU/ml, luteinizing hormone (LH):0.29 mIU/ml, dehydroepiandrosterone sulphate: 0.7 ug/dl, testosterone: 0.0 ng/ml. Her thyroid functions were normal. Cancer antigen-125 (CA-125) was high, with 213 U/ml (normal values:0-35 U/ml), but other tumor markers such as alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) were within normal limits. Luteinizing hormone-releasing hormone (LHRH) stimulation test was performed without an increase in LH and FSH. Radiological examination revealed a large, cystic and solid lesion (12x9cm) in the umbilical and infraumbilical regions. The origin of the mass was not detected ultrasonographically (Figure 2). The size of uterus was big for the patient's age, and there was free pelvic fluid. Subsequently, magnetic resonance imagining (MRI) of the abdomen and pelvis showed a huge, 12x9x5 cm (APxTRxCC) lesion of fluid consistency arising from the pelvis (Figure 3 and 4). The ovaries were not visualized, possibly due to this huge mass. Thorax contrast-enhanced computed tomography was performed for staging and there was no sign of metastasis. Positron emission tomography was obtained, and no distant metastases were shown. MRI of the brain and hypothalamic-pituitary region was normal. Based on imagining features and laboratory findings, the diagnosis of the mass was unclear. So, we recommended diagnostic and therapeutic laparotomy. Laparotomy was performed under general anesthesia. An ovarian mass on the left, with a diameter of 12x9 cm, was detected and completely resected along with the left ovary. The right ovary was normal. On gross examination, the tumor was seen to originate from the left ovary, which now consisted of a gray mass with solid and cystic components (Figure 5). Pelvic fluid was aspirated and sent to cytology. No lymphadenopathy was detected in the pelvic area. The mass was sent for histopathological examination. Grossly, a large, intact ovarian tumor with a grey-white fibrous capsule, measuring 14x8x6 cm and weighing 560 grams, was resected. The sagittal surface was heterogeneous, showing creamy nodular areas and small cystic structures. The microscopic appearance was characterized by a proliferation of the sex-cord stromal cells with high mitotic activity (7-8 mitosis per 10 high power fields) and high-grade cell atypia. Immunohistochemical staining was positive for inhibin, calretinin, cluster of differentiation (CD)99 and smooth muscle actin (SMA). The cells were focally positive for pancytokeratin. The tumor was negative for CERB2, CD10, EMA, AFP and hCG. No Call-Exner bodies were identified. The ovarian capsule had ruptured, and malignant cells resided within the pelvic fluid. The final diagnosis was a juvenile granulosa cell tumor. The tumor was allocated as FIGO (International Fedaration of Gynecology and Obstetrics) stage IC and she was treated with bleomycin, etoposide, cisplatin (BEP) chemotherapy for four cycles. Response to treatment was good after 18 months after the surgery with regression in breast size and decrease in serum CA-125 levels. There were no signs of re-occurrence of tumor and control ultrasonography was normal. Informed consent was obtained from the parents.

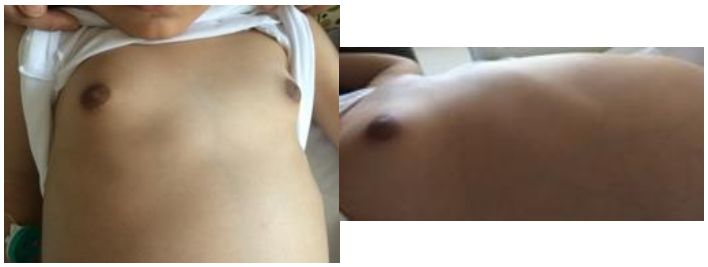

Figure 1: Breast enlargement and alveolar pigmentation

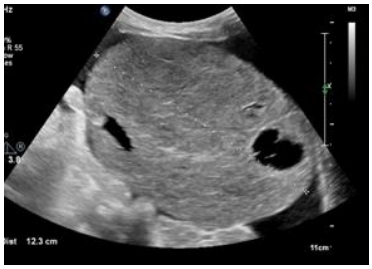

Figure 2: Ultrasonographic imaging

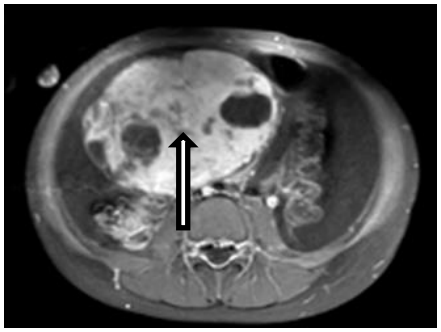

Figure 3: The axial view of an abdominal MRI (Arrow: mass)

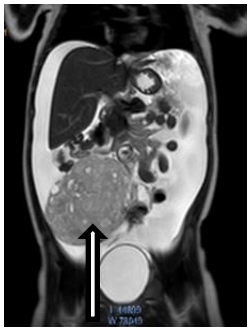

Figure 4: The coronal view of an abdominal MRI (Arrow: mass)

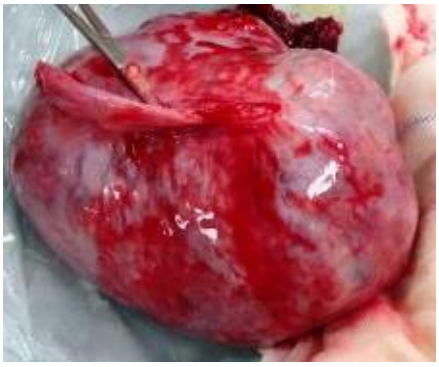

Figure 5: Intraoperative view of the ovarian tumor

Discussion

Precocious puberty in girls is generally defined as appearance of secondary sexual characteristics before eight years of age. Precocious puberty is divided in two as central precocious puberty (CPP) and peripheral precocious puberty (PPP). CPP results from premature activation of the hypothalamus- pituitary-gonadal axis. The majority (74%) of

girls have idiopathic CPP, but it can be secondary to an underlying disorder [4]. PPP results from sex steroid exposure by a process other than activation of the hypothalamus- pituitary-gonadal axis. It is much less common than CPP [5].

Ovarian tumors are uncommon in the pediatric population, with an estimated incidence of 2.6 cases per 100.000 girls per year. Ovarian tumors in children and adolescents are reported in 10-20% of all ovarian masses or neoplasms and comprises approximately 1-2% of all childhood malignancies [6].

Granulosa cell tumors are rare sex cord stromal tumors, encompassing 1-5% of all ovarian tumors [7]. They are classified into juvenile and adult types [1]. The adult type of GCTs is the more common type, accounting for nearly 95% of all GCTs. They usually present in women over 40 years of age [2]. Juvenile types constitute only 5% of GCTs and occur in prepubertal girls and in women younger than 30 years, with a mean age of 13 years [2,8]. JGCTs can be hormonally active, secreting estrogen and causing 10% of all cases of precocious puberty in premenstrual females [2,7].

We herein describe a rare case of JGCT in a 4-year-old girl presenting with isosexual precocity as premature thelarche. She had an abdomino-pelvic mass without abdominal pain. Her serum laboratory findings were consistent with peripheral precocious puberty, with high estradiol levels. CA-125 was also high. Since we did not know the exact histopathology at the time of diagnosis, we did not measure inhibin levels. On the third postoperative day, inhibin A was normal (1 pg/ml), along with other sex hormones and tumor markers, which were all within normal range.

Patients with recurrent or persistent ovarian cysts, especially with a significant solid component beyond three months, should alert the clinician to the possibility of an ovarian tumor, and JGCT [9]. In our case, it was the patient's first visit and she had no past medical history. The abdomino-pelvic ultrasound showed a huge cystic and solid lesion of 12 cm in diameter. The left and right ovaries were not visualized. The uterus was oversized for the patient's age. MRI of the abdomen and pelvis confirmed ultrasonographic findings. With high levels of CA-125, our preliminary diagnosis was an ovarian tumor.

Imagining characteristics of adult and juvenile GCTs are non-specific and these tumors cannot be reliably distinguished from other ovarian tumors on imaging alone [10]. The evaluation of sex hormones and serum tumor markers can be useful for the differential diagnosis in pediatric ovarian masses. In our patient, laboratory findings were more helpful for the diagnosis compared to imagining. Our patient presented with alveolar pigmentation, breast enlargement, advanced bone age and accelerated height and weight gain. These were seen due to tumor-derived estradiol.

At presentation, 90% of JGCTs are FIGO stage I, confined to the ovary, and have a good prognosis with a 5-year survival rate of 90%. They are curable with conservative surgery alone. However, patients with advanced disease or tumors with high mitotic activity have poorer prognosis and maybe treated with chemotherapy [11].

Precocious puberty has been previously reported in some girls with JGCTs. Abdominopelvic ultrasonography should be performed in all females with PP. After detecting ovarian tumor, serum tumor markers should be evaluated along with serum sex hormones.

Ovarian tumors at all ages are treated by oophorectomy or salpingo-oophorectomy and surgical staging. The prognosis of ovarian tumors in children is excellent if they are detected in early stages [12].

Outcomes tend to be less favorable in the presence of a large tumor size (10-15cm) or tumor rupture [13]. Other unfavorable prognostic factors may include nuclear atypia, high mitotic rate, extra-capsular extension of tumor within the ovary, and presence of residual disease after surgery [7]. The median time to relapse is approximately four to six years after initial diagnosis [14]. Tumor markers such as inhibin can also be used to asses for recurrence [15].

Conclusion

JGCTs are rare causes of peripheral precocious puberty. In initial stages, survival time is long and fertility sparing surgery can be safely preferred since most of the patients are young. Serum sex hormones, tumor markers, and inhibin can be used to asses diagnosis and recurrence.

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This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine