

Granulosa cell ovarian tumor: precocious puberty in infant less than 1 year of age. Case report

Tumor de las células de granulosa: pubertad precoz en lactante menor de 1 año. Caso clínico

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Abstract

Introduction: Juvenile granulosa cell tumors (JGCT) are very rare, especially in infants under the age of one. The most frequent presentation is with signs of precocious puberty. **Objective:** Present an infant with peripheral precocious puberty, diagnosis of JGCT and follow up. **Clinical case:** 10-month-old female infant with thelarche, pubic hair and palpable abdominal mass accompanied with elevated levels of estradiol, very low gonadotrophins and images that show a very large ovarian mass. A salpingo-oophorectomy was carried out with full regression of symptoms and signs and improvement of laboratory exams. The biopsy showed TCGJ so inhibin B (InB) was taken as tumoral marker after surgery. This hormone was high initially, but rapidly declined. Follow-up was based on InB, antimüllerian Hormone (AMH) and estradiol as described in this type of tumors. **Conclusions:** Juvenile granulosa cell tumors are very infrequent in pediatric age, but should be suspected in girl with peripheral precocious puberty. The majority of cases improve with surgery, but strict surveillance of tumoral markers is needed. The most specific markers are inhibin B and anti müllerian hormone (AMH), followed by estradiol levels.

Keywords:

Granulosa cell ovarian tumor;
peripheral precocious puberty;
inhibin B;
anti müllerian hormone

Introduction

The precocious puberty is unusual in females younger than 1 year. The differential diagnosis must be made between central precocious puberty against peripheral precocious puberty.

Regarding the central precocious puberty, the main cause in the infant is/are hypothalamic tumors (hamartomas), while in older females it is idiopathic. In the peripheral precocious puberty, there is an ovarian activation due to the McCune Albright Syndrome, cysts, ovarian tumors or an exogenous administration of estrogens. The differentiation between both types is based on the measurement of gonadotropins and estradiol, which can be difficult to detect in infants younger than 2 years due to “mini-puberty”, a condition accompanied with high values of the said hormones¹.

One percent of pediatric tumors are from an ovarian origin and 60% of them correspond to neoplasms originated from germinal cells²⁻¹⁴. Less than 8% are secondary tumors due to sex-cord stromal²⁻¹³. The embryogenic sex-cord result in granular cells tumors, stroma and theca cell tumors². Thus, tumors in sex cords are due to these cells, being the granular cell tumors the most frequent (90%)³.

The granular cells represent the somatic components in the follicles and their function is to produce sex steroids and the growth factors necessary to perform the folliculogenesis and ovulation. The clinical and histopathological characteristic described two sub-types of granular cells tumors: an adult type and a youthful type³⁻¹⁰. The adult type is the most common (95%), with an average age of presentation between 50-54 years; while the youthful type (5%) (TCGJ) is diagnosed principally in children younger than 10 years²⁻¹⁴. Both can occur in both age groups, but it is quite uncommon. The reports from the TCGJ of chil-

dren younger than 1 correspond to less than 10% of the total³.

The precocious thelarche, areolar pigmentation, genital bleeding and secretions, and abdominal mass are the most common clinical symptoms present in pre-pubertal females.

We show an infant with peripheral precocious puberty due to TCGJ, with the objective of highlighting the keys to diagnosing it, its treatment and follow-up.

Clinical Case

The patient was a 10-month old girl, who assisted to endocrinology due to present thelarche and pubic hair 4 and 2 months of evolution, respectively, along with apocrine odor and whitish vaginal discharge.

The patient had no perinatal or morbid records of relevance, no use of medicine or products with phytoestrogens. The physical exam showed: weight 23lb (10.5 kg), size 29.9in (76 cm), size/age index (p) 96 and size/weight index p89 (WHO reference). The patient had pale skin, without light brown stains. The patient's abdomen was globular and it was possible to feel a mass, 10 cm below the costal margin with an increased consistency. She had breasts scale 3 in the Tanner scale (T) (3.5 cm of diameter, dark areolas, abundant pubic hair TIII; however, it was thin, long and dark, in all the mons pubis. Her genital were estrogenized, with a normal clitoris (Figure 1).

We considered a precocious puberty diagnose, because of said records, we also requested a study with laboratory tests. The tests showed: low number of gonadotropins, estradiol (457 pg/mL) and a low LDH (2,690 mUI/mL) (Table 1).

The abdominal and pelvic ultrasonography (US) showed a big solid-cystic abdominal mass (Figure 2).



Figure 1. Tanner III breasts (breast extends beyond the areola with no separation of contour), large pigmented areolas. Pubic Hair Tanner III (dark hair on pubis) and estrogenized genitalia (increased thickness of the mucosa, pallor, and no secretion).

Table 1. Diagnosis: Initial test results

	Result	Reference values
Hematocrit (%)	27.6	33-37
Hemoglobin (gr/%)	8.3	10-11
LDH (mUI/ml)	2.690	210-420
AST (U/L)	58	5-32
ALT (U/L)	16	7-33
GGT (U/L)	14	5-27
Estradiol (pg/ml)	457	< 12
LH (mUI/ml)	< 0.5	0.02-0.3
FSH (mUI/ml)	0.66	0.2-4
Testosterone (ng/ml)	25	0.2-0.6
DHEA-S (ug/dL)	38.2	5-48
Androstenedione (ng/ml)	1.06	0.06-0.6
17-hydroxyprogesterone (ng/ml)	0.77	0.1-10
TSH (mUI/L)	1.84	0.9-7.7
T4L (ng/dL)	1.19	0.9-2.6
βHCG (mUI/mL)	2.3	< 5
CEA (ng/mL)	1.0	< 5
α feto protein (ng/mL)	10.7	< 40

LDH: lactate dehydrogenase deficiency; LH: luteinizing hormone; FSH: follicle stimulating hormone; DHEAS: dehydroepiandrosterone sulfate; TSH: thyroid stimulating hormone; T4L: free thyroxine; βHCG: human chorionic gonadotropin; CEA: carcinoembryonic antigen.

The CT scan confirmed the presence of a big abdominal expansive process (15 x 13 x 12 cm), with a great effect of mass and a complex structure, probably from an ovarian origin (Figure 2). The uterus had an increased size (7 cm long), a significant thickening in the endometrial cavity. The annexes were not identified.

After ten days from the first consultation, we performed a left salpino-oophorectomy and a resection of the big adnexal mass (800 grams) (Figure 3). The histological study showed a tumor formed of big and medium cells, of moderate to abundant granular cytoplasm and nucleus slightly oval/pleomorphic, some showed the presence of follicles of different sizes, on lax stroma, oedematous. The findings of the histology were compatible with TCGJ (Figure 4).

The patient evolved and there was a regression of the pubertal signs and of the ultrasonographic alterations. Two months after the surgery, a control with CT showed no pathological findings.

Two years later, the patient showed TIII breasts and vaginal discharge. We performed a pelvic US, which showed a 2.6cc increase in the volume of the right ovary. There was a spontaneous regression of the symptoms with tumor markers. The GnRh test had low values, the pelvic US and the bone age were normal, therefore, we diagnosed non-specific transient thelarche (Table 2).

Figure 2. Ultrasound (A, B) showed a large solid abdominopelvic mass with cystic areas inside. Computed tomography in axial (C), coronal (D) and sagittal (E) sections confirmed a large expansive process of 15 x 13 x 12 cm involving abdomen and pelvis, with a heterogeneous structure, and mass effect on the contiguous structures (arrows), enlarged uterus with endometrial thickening (arrowheads).

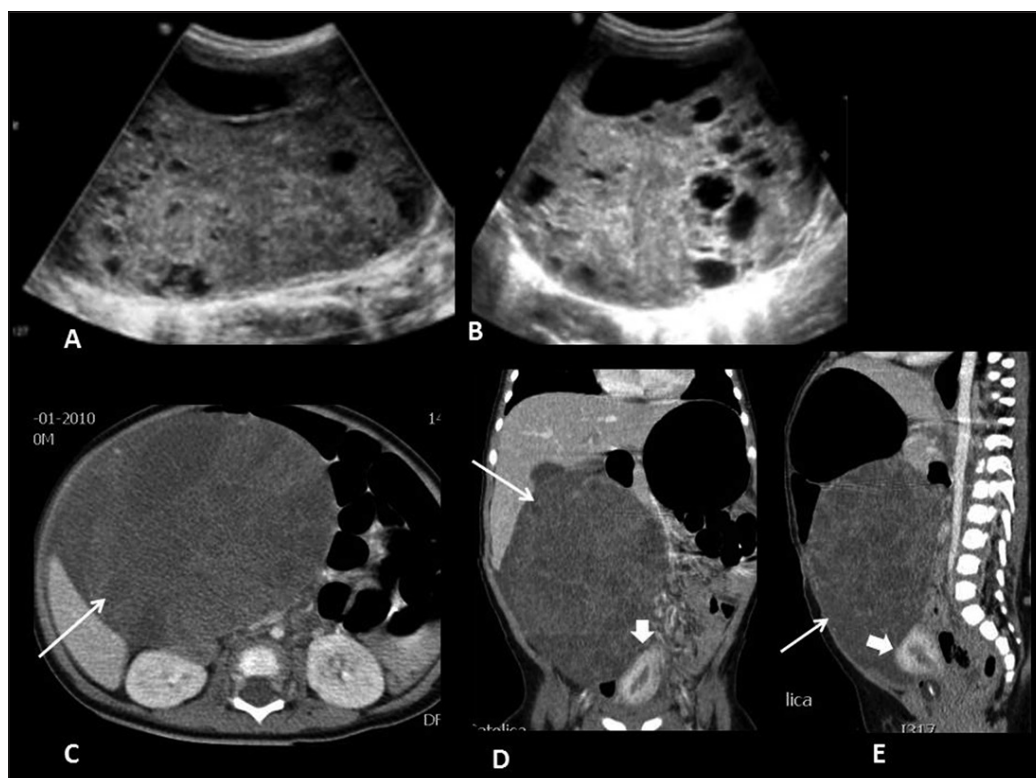




Figure 3. Left adnexal mass of 800gr, signs of necrosis and hemorrhages are seen on it.

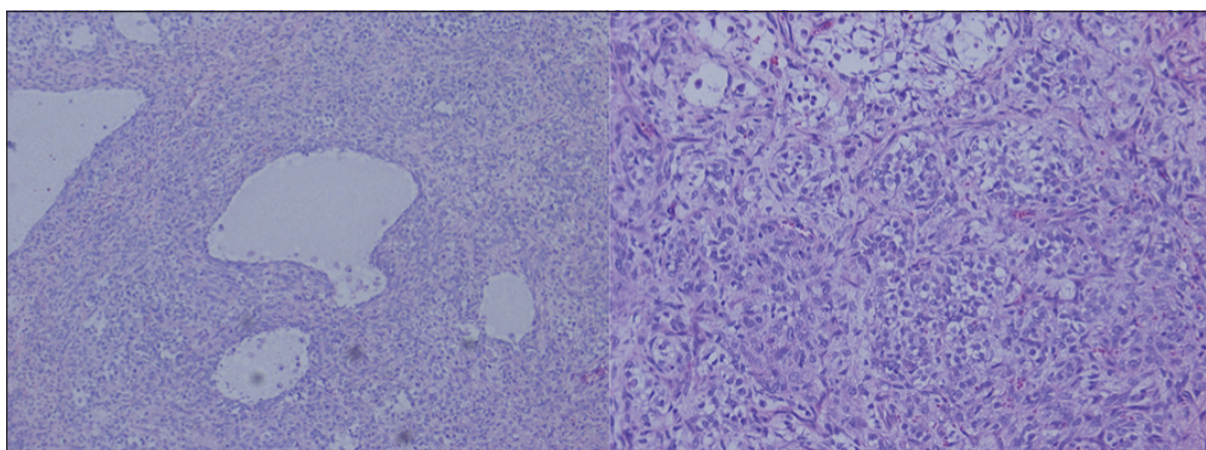


Figure 4. Histopathological image: abundant granular cytoplasm and pleomorphic ovoid nuclei with the presence of follicles of different sizes.

Table 2. Follow-up test

Age	10 months	18 m	2 y	3 y 4 m	4 y	5 y	5 y 6 m
<i>Estradiol</i> (pg/ml) (NV < 12)	457	15	7			6	< 5
<i>Inhibin B</i> (pg/ml) (NV < 44)		50	17				10,8
<i>AMH</i> (ng/ml) (NV 0.5-4.7)			1.24	1.23	1.26		
<i>GnRH test</i>							
LH peak			2.2				
FSH peak			45				
<i>Bone age</i>	1 y		2 y				6 y

NV: normal values; GnRH: gonadotropin-releasing hormone; AMH: anti-mullerian hormone; LH: luteinizing hormone; FSH: follicle stimulating hormone.

The regular measurement of Inhibin B (InB), Anti-Müllerian Hormone (AMH) and estradiol was normal (Table 2).

During the 4th year of monitoring (5 years old), the patient had an apocrine odor for 3 months of evolution, without breast development or pubic hair. The pelvic US showed a normal uterus and a right ovary (1.7 cc).

Discussion

The form of presentation of TCGJ is the peripheral precocious puberty, being the premature thelarche, areolar pigmentation, whitish vaginal discharge, genital bleeding and pubic hair the most common symptoms²⁻¹³. Along with the findings of the abdominal mass, and sometimes, abdominal pain and ascites²⁻¹²⁻¹⁴. Only a few cases become complicated due to tearing or twisting (6%)²⁻¹⁴. In the history, there is an increase in the growth and an advanced bone age¹¹. Most of the cases present large and unilateral tumors, 4.7 in (12 cm) on average (1.1-12.7 in / 3-35 cm)².

Regarding the laboratory tests, it is possible to observe an increase in the levels of estradiol, there is no contaminant increase of the gonadotropins, which are restrained due to the negative feedback of the estrogens. Granular cells secrete a large number of estrogens due to the overexpression of the aromatase enzyme, which stimulates the transformation of androgens into estrogens¹⁴. The estradiol is responsible for symptoms of this disease; however, it is not useful as a marker in the follow-up due to the late increase³.

The Inhibin is synthesized by granular cells and it expresses itself in the follicles. It presents paracrine and autocrine action and also regulates the secretion and synthesis of FSH. There are two sub-types (A and B), although it secretes, mainly, Inhibin B, thus, its determination is useful as a tumor marker in the monitoring²⁻⁴.

The AMH is also, co-secreted by these cells, however, the produced amount is increased during the reproductive period; it controls the formation of primary follicles. It also works as a marker, although with a lower value in comparison with the previous one²⁻⁴.

The image test must include an abdominal and pelvic US, and a magnetic resonance imaging (MRI) or CT. Even though it can show up as a solid mass or as a cystic mass, it is more common when it has both components, which occurs both in the adult and youthful type². Typically, it shows up as a large, unilateral mass with a multi-cystic aspect, the irregular septum in the inside, with or without hemorrhage, which is associated with the uterus growth and the endometrial thickening, due to the estrogenic effect⁶⁻¹⁴ (Figure 2). In the anatomopathological study, the youthful type shows

up with encapsulated tissues, unilateral, and solid with cystic zones of hemorrhagic content. Microscopically, it is possible to observe micro and macro-follicles in the nodular formations. This and the absence of Call-Exner bodies are two of the characteristics that differentiate it from the adult type²⁻¹⁰.

These tumors can be classified by the category FIGO from I to IV 9-10-14, which is related to the prognosis. Stage I correspond only to the ovary involvement. Most of the TCGJ are diagnosed in stage I, where the mortality is very low, they do not require complementary therapies and they have a good prognosis on a 5-year term (90-100%)¹²⁻¹⁴. Oncological monitoring and the use of chemotherapy are only required in advanced stages, in other words, surgery on early stages is curative²⁻⁷⁻⁸⁻¹⁴.

The patient showed a peripheral precocious puberty due to TCGJ, the key for diagnosing was the mass with high levels of estradiol, but with suppressed gonadotropins. The prognosis is very good since the disease was on stage I. A follow-up with Inhibin B or AMH is recommended, every 6 months per 2 years, then on an annual basis, without relapses in almost 4 years after the surgery.

Conclusion

The peripheral precocious puberty is an unusual clinical condition in the pediatric area, especially in children younger than 1 year. The excessive breast development, along with other symptoms of pubertal development which can demonstrate the presence of this pathology, therefore, the tests to demonstrate it must be performed. If the disease is detected early, a surgery will be definitive treatment, and there will be a good prognosis on a long-term basis. Patients must have a strict control with images and markers, such as Inhibin B and AMH.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

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Conflicts of Interest

Authors declare no conflict of interest regarding the present study

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