

CASE REPORT

A rare case of ovarian juvenile granulosa cell tumor in an infant with isosexual pseudo puberty and revision of literature

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Abstract. Juvenile ovarian granulosa cell tumors (JGCTs) are described infrequently in pediatrics, and their finding in infants is exceptional. We highlight the presenting symptoms, radiologic images, operative management, and histopathologic findings of a 9-month-old female with isosexual pseudo-puberty. An updated revision of literature in infants below the age of 12 months is also reported. (www.actabiomedica.it)

Key words: Precocious puberty, infant, ovary, granulosa cell tumor, estrogen.

Introduction

Ovarian neoplasms are infrequent in childhood, with an incidence of only 1–5% (1). They can be classified as epithelial, germ cell, or stromal. Within the stromal category, the most common tumor is the granulosa cell tumor (GCT). The juvenile subtype accounts for 5% of these cases. Juvenile granulosa cell tumours (JGCT) are defined as a variant form of adult granulosa cell tumors, as they have different clinical and pathologic features (2). In infants, less than 1-year JGCT is extremely rare, with very few reported cases in the literature (3). In this case report, we highlight the presenting symptoms, radiologic images, operative management, and histopathologic findings of a 9-month-old female with isosexual pseudo puberty.

Case presentation

A 9-month-old girl born at term presented with a day history of bloody vaginal secretions. The diaper

was stained with streaks of blood mixed with mucus. The mother noticed, 2 months before, bilateral breast development and the presence of fine hair growth in the genital area. Parents were non-related, and they had no family history of endocrine disease or precocious puberty.

On physical examination, the child had no dysmorphic features. Her length and weight were in the normal range [75cm (1.66 SD) and 10.4 kg (1.85 SD), respectively]. She had no skin hyperpigmentation, no skeletal abnormalities, or dysmorphic features. The abdomen was soft with no organomegaly or palpable mass. Breast development corresponded to Tanner's stage 2 and fine pubic hair was evident. No neurological abnormalities were detected. The rest of the clinical examination was unrevealing.

Endocrine workup revealed elevated levels of estradiol (E2), anti-Mullerian hormone (AMH), inhibin A and B, and androstenedione. The luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were suppressed (Table 1).

Table 1. Hormonal assessment and alpha fetoprotein at presentation.

Test	Value	Normal Range
Androstenedione	6.8 nmol/L (High)	0.0-3.0
Dehydroepiandrosterone -sulfate	0.320 μ mol/L (Normal)	0.090-3.350
Estradiol	1,091.0 pmol/L (High)	0.0-132.0
Follicle Stimulating Hormone	<0.3 IU/L (Low)	1.2-12.5
Luteinizing Hormone	<0.3 IU/L (Low)	0.3-2.5
Anti-Mullerian Hormone	>1714.0 pmol/L (High)	0.1-38.6
Thyroid Stimulating Hormone	2.77 mIU/L (Normal)	0.70-8.40
Testosterone Level	2.2 nmol/L (Normal)	0.0-2.2
Beta human Chorionic Gonadotropin	0.9 IU/L (Normal)	0.0-5.0
Alpha Fetoprotein	6 kIU/L (Normal)	1-33
Serum Inhibin A	385 pg/ml (High)	<4.7
Serum Inhibin B	3805 pg/ml (High)	<111

An abdominopelvic ultrasound showed a relatively well-defined round-shaped heterogeneous hypoechoic lesion measuring 5.4 x 4.0 x 5.4 cm (volume of 60.6 ml). The mass had a solid appearance with some internal vascularity but no calcifications. Uterus

was enlarged (5.2 x 2.4 x 2.3 cm), with trace fluid in the uterine cavity (Figure 1).

Bone age assessed with Greulich and Pyle female standard was advanced by 1.8 years (+4 SD) (Figure 2). Due to concern for an ovarian tumor,

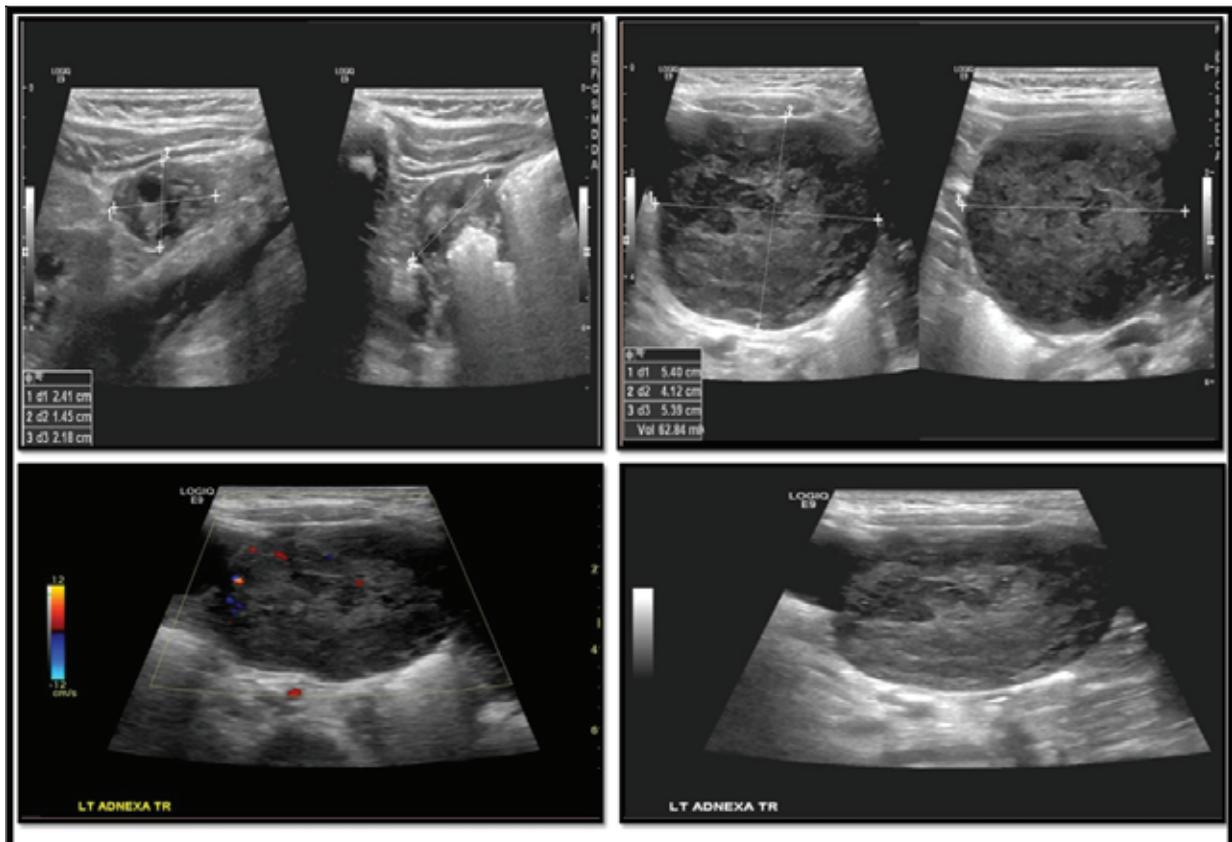
**Figure 1.** Pelvic ultrasound showing a large solid abdominopelvic mass with cystic areas inside.



Figure 2. Advancement of bone age 18 months (3.4 SD) according to Greulich and Pyle female standard.

magnetic resonance imaging (MRI) of the abdomen and pelvis with intravenous contrast was requested. MRI confirmed a large solid lesion in the left-sided adnexa, measuring 5.4 x 4.12 x 5.39 cm (volume of 62.84 ml), with significant gadolinium enhancement

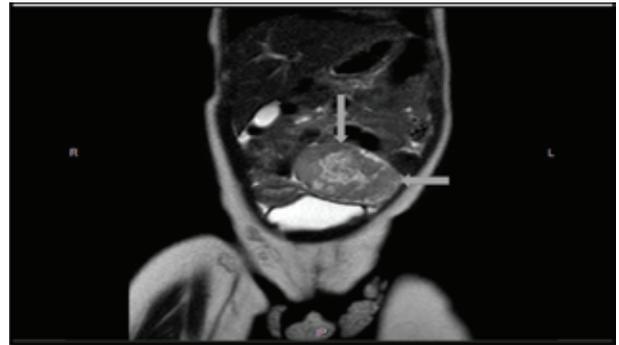


Figure 3. Coronal MRI of the abdomen and pelvis showing large solid lesion in the lower abdomen and pelvis. The mass was thought to originate from the left ovary.

and minimal central necrosis (Figure 3). Given the elevated serum inhibin B and estrogen levels, a suspected diagnosis of JGCT was done. Chest computed tomography was normal.

An exploratory laparotomy via a midline incision was performed. An ovarian mass was detected and tumor resection with left total salpingo-oophorectomy was done. The tumor was ovoid, encapsulated with smooth-surface measuring 6.5 x 4 x 6.5 cm and weighing 75 grams. It was solid, yellow, with a nodular cut surface. Haemorrhage, necrosis, or cystic changes were not present. (Figure 4). Separate specimens were taken

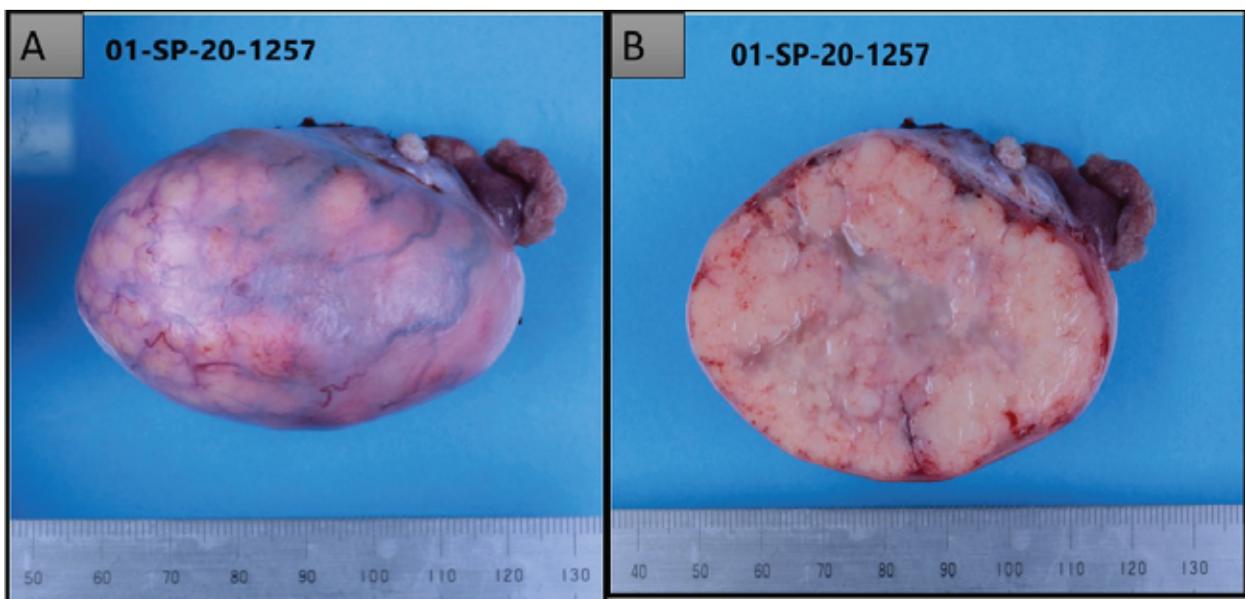


Figure 4. A: Gross appearance of an ovarian juvenile granulosa cell tumor (JGCT), measuring 6.5 x 4 x 6.5 cm and weighing 75 grams with fallopian tube 5 cm long attached, in a 9-month-old female infant B: Cross section of the resected ovarian JGCT showing solid yellow, nodular cut surfaces with no necrosis.

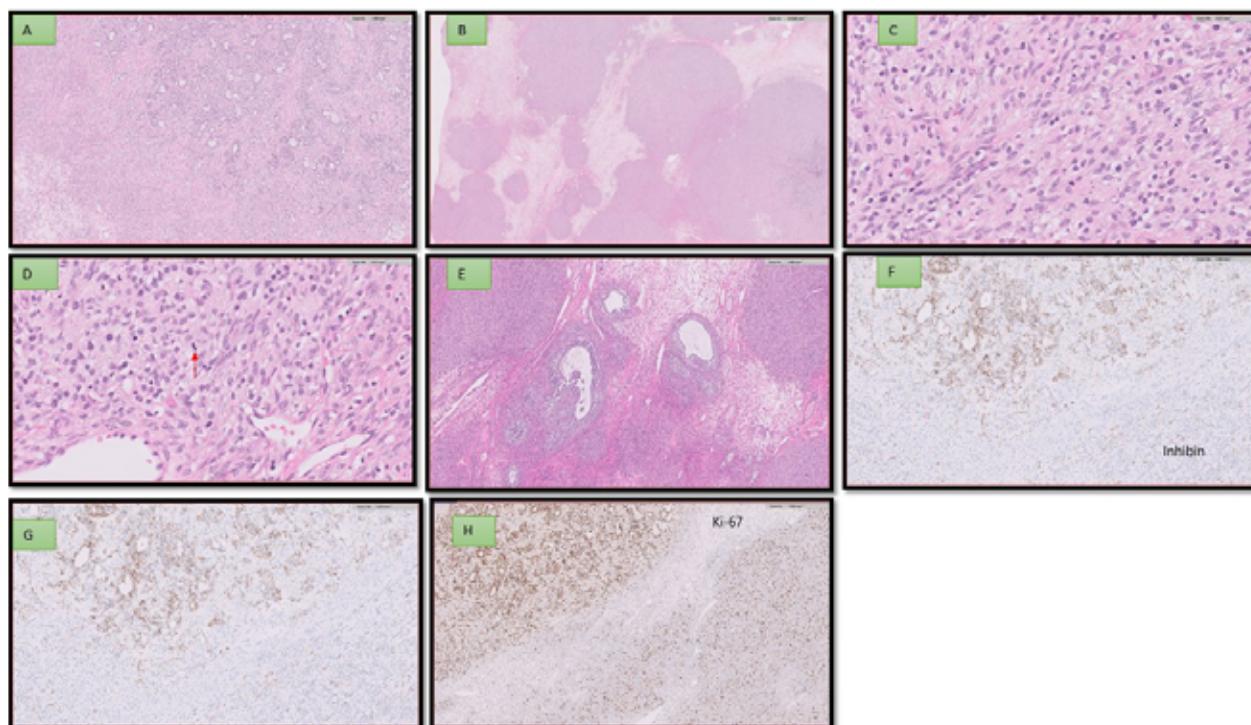


Figure 5. Hematoxylin and eosin staining of JGCT tissue showed granulosa cells lining the spaces and spindle shaped cells with moderate numbers of mitoses forming the solid areas of the tumor. Immunohistochemistry showed positive staining for Calretinin and moderately extensive staining for the proliferation marker Ki-67. The inhibin immune stain was positive in the cytoplasm of very many of the ovarian tumor cells with a mild to moderate intensity.

for histopathology from the left ovary, left fallopian tube, peritoneum, round ligament and omentum. The postoperative course was uneventful, and the patient was discharged on the third postoperative day.

Histopathology revealed a granulosa cell tumor compatible with a juvenile type of stage 1a, according to the International Federation of Gynecology and Obstetrics (FIGO) classification for ovarian tumors. Immunohistochemical analysis of the tumor showed positive staining for calretinin and inhibin A (Figure 5). The final diagnosis was JGCT. No chemotherapy or radiotherapy was required.

During her follow-up, at 1 week and 1 month after hospital discharge, and hormonal testing revealed a prepubertal level of E2 and a decrease of AMH and inhibin levels (Table 2). Breast development regressed significantly within 6 months. After 12 months of follow-up, the patient had no evidence of disease recurrence.

Discussion

Although granulosa cell tumors can occur at any age, they present most often in women of reproductive age and they occur as well as in women who are postmenopausal (4). The annual incidence of JGCT in the United States is 0.4–1.7/ 100,000/y. The incidence of tumors in women of European and American backgrounds is almost twice that of women of African and Asian origin, 0.98 versus 0.522/100 000/y (5-7).

The ovarian neoplasms in preadolescent girls 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 0.102/100,000 in less than 9 years of age as compared to 1.072/100,000 in those between 10 and 19 years. In all age groups, the usual pathology is germ cell tumor (1).

Table 2. Hormonal follow-up at 1 week and 1 month post-operative.

Test	Value 1 week after the surgery	Value 1 month after the surgery	Normal Range
Estradiol	62 pmol/L (Normal)	< 55 pmol/L (Normal)	0.0-132.0
Anti-Mullerian Hormone	9 pmol/L (Normal)	9 pmol/L (Normal)	0.1-38.6
Beta human Chorionic Gonadotropin	0.8 IU/L (Normal)	< 0.6 IU/L (Normal)	0.0-5.0
Alpha Fetoprotein	4 kIU/L (Normal)	4 kIU/L (Normal)	1-33

Table 3. Revision of literature, from 1998 to 2021, of juvenile granulosa cell tumor (JGCT) reported in infants.

Authors and references	Age (months)	At presentation	Hormonal assessment
Imai A et al. <i>Gynecol Oncol.</i> 1992; 46:397-400.	10	Premature thelarche and adrenarche	Elevated level of serum estradiol
Cameron FJ et al. <i>Acta Paediatr.</i> 1997; 86:1016-8.	Infant	Signs of puberty	Marginally elevated serum α -fetoprotein level
Leyva-Carmona et al. <i>J Pediatr Hematol Oncol.</i> 2009;31: 304-6.	2	Abdominal distention	Not available
Sivasankaran S et al. <i>J Pediatr Adolesc Gynecol.</i> 2009; 22:e 114-7.	10	Premature thelarche and adrenarche	Elevation of estradiol, inhibin B, total and free testosterone
Leyva-Carmona et al. <i>J Pediatr Hematol Oncol.</i> 2009;31: 304-6.	Newborn with Ollier disease	Abdominal mass and rupture of left ovarian tumor	Not available
Wang Y et al. <i>J Pediatr Hematol Oncol.</i> 2011;33: 241-5.	8	Abdominal mass	Not available
Hamdane MM et al. <i>Pediatr Surg</i> 2012; 47:269-70.	11	Distended abdomen, constipation, fever, and poor health	Not reported
Lacourt P et al. <i>Rev Chil Pediatr.</i> 2017; 88:792-7.	10	Thelarche, pubic hair and palpable abdominal mass	Elevated levels of estradiol, very low gonadotrophins
Vasileva P et al. <i>Akush Ginekol (Sofia).</i> 2000;39: 54-6.	10	Isosexual puberty and presence of ascites	Not available
Anbarasu CR et al. <i>J Pediatr Surg Case Rep.</i> 2020;59: 101481.	5	Acute abdomen and rupture of tumor	Not reported

JGCT represents a unique subtype of tumors, classified as a low to moderate grade of malignancy. They are usually diagnosed at the mean age of 13 years but the incidence in infants is very rare (8). In a review of the medical literature performed in 1997 by Bouffet et al. (9), 36 cases of JGCT were reported before the age of 2 years, 21 is younger than 1 year. Since then, only a few more cases have been reported (10-13). An update of cases diagnosed in infants (less than 1 year) from 1997 to 2021 is summarized in table 3.

The presentations of JGCT is variable, ranging from isosexual precocious pseudo-puberty such as breast enlargement, pubic hair development, increased

vaginal secretions, and vaginal bleeding, advanced somatic development, areolar pigmentation, and other secondary sex characteristics due to a hyper estrogenic state to life-threatening acute abdomen due to tumor rupture (Table 3).

Abdominal symptoms may favour earlier detection, leading to more timely surgical management and a more favourable prognosis (8).

JGCT has also been associated with various congenital anomalies including Ollier disease, Maffucci syndrome, leprechaunism, Potter syndrome, hypercalcemia, Peutz-Jeghers syndrome, and cytogenetic aberrations (8).

Our patient presented with the development of secondary sexual characteristics (breasts and pubic hair) that occurred as early as 7 months of age and vaginal bleeding at 9 months of age. Her tumor size was noticeable only through ultrasonographic evaluation.

Evidence of rapid growth has been reported in few cases with similar conditions. However, our patient had a length SD of 1.66 with markedly advanced bone age (+ 3.4 SD). This clearly demonstrated a marked effect of high sex steroid (E2) on skeletal maturation very early in life. Elevated serum estradiol is a uniform lab finding, although there have been some cases reported of low or normal E2 concentrations (8).

Serum inhibin concentration is elevated in almost all cases. In our patient, inhibin level was significantly elevated pre-operatively and decreased to normal after surgical resection of the tumor.

Inhibin is synthesized by granular cells and it expresses itself in the follicles. It presents paracrine and autocrine actions and also regulates the secretion and synthesis of FSH. There are two sub-types (A and B). Granulosa cells secrete mainly inhibin B, which makes its determination useful as a tumor marker in the diagnosis and monitoring (14).

The AMH is also, co-secreted by granulosa cells. Its secretion is augmented during the reproductive period. It controls the formation of primary follicles. Its normalization occurred one week after surgery and provided us its value as a good biomarker for tumor monitoring (14).

Additionally, immunohistochemistry is a useful adjunct for diagnostic confirmation because the tumor is typically immunoreactive for inhibin and/or calretinin. The histopathology of the tumor of our patient showed a positive reaction to inhibin. Despite histologic features associated with malignancy, such as nuclear atypia and high mitotic activity, JGCT usually has a benign clinical course. Surgical resection is the treatment of choice for JGCT, and the prognosis in infancy is excellent. Most cases, as in our infant, are unilateral and limited to the ovary at diagnosis, placing them in FIGO stage 1A.

For these tumors, complete resection via unilateral oophorectomy or salpingo-oophorectomy appears to be curative, regardless of tumor size and histopathologic features. In our patient, complete removal of the tumor with unilateral salpingo-oophorectomy was

performed with complete return of all hormones to normal prepubertal levels.

The most important prognostic factor is the tumor stage. If the tumor stage is IA, the survival rate is 83–98% while the overall survival rate for all stages is 78–92% (7). Other characteristics that may confer a favorable prognosis include age less than 10 years and presentation with precocious puberty, as occurred in our infant (10).

Recurrence is rare and related to the stage at diagnosis. Cases of recurrence have been reported up to 3 years after the initial surgery, so tumor surveillance is important. Hormone levels, most commonly serum inhibin concentration, should return to normal post-operatively and can be used to assess response to treatment and monitor for recurrence and spread (8).

Conclusion

JGCT is a rare ovarian neoplasm in infants. The prognosis is favourable in patients who have only ovarian involvement and when they are treated early with surgery.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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