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A 12-Year-Old Girl with Juvenile Granulosa Cell Tumor of the Ovary, Presenting with Adolescent Hyperprolactinemia, Galactorrhea, and Amenorrhea

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 12-year-old
Final Diagnosis: Juvenile granulosa cell tumor
Symptoms: Abdominal pain • galactorrhea • secondary amenorrhea
Medication: —
Clinical Procedure: —
Specialty: Pediatrics and Neonatology • Surgery

Objective: Rare disease

Background: Juvenile-type granulosa cell tumors (JGCTs) are a rare subtype of sex cord stromal tumor with a characteristic histology that is commonly found in the first 3 decades of life. It most commonly presents with symptoms of hyperestrogenism, which may present as precocious pseudopuberty or as menstruation-related symptoms, allowing for early detection of the tumor.

Case Report: We present the case of a 12-year-old girl who presented to her primary care provider (PCP) with secondary amenorrhea with intermittent abdominal pain, who underwent an ultrasound for further evaluation, which revealed a large incidental pelvic mass. She was admitted to the Emergency Department (ED) and had findings of galactorrhea and hyperprolactinemia on examination. Imaging studies demonstrated a large ovarian mass measuring 15.0×9.0×18.8 cm that was resected, and subsequent pathology results showed JGCT stage 1A.

Conclusions: Prognosis of granulosa cell tumors (GCT) largely depends on its initial size, stage at diagnosis, residual tumors after surgery, and the subtype of GCT. If the patient is of reproductive age, fertility-sparing surgical options must be considered and patients must be regularly monitored for recurrence. JGCTs can present with minimal to no symptoms of precocious puberty in young girls but may present with amenorrhea, which may be considered normal for their developmental age. Although JGCTs are rare, they are important to include in differential diagnoses of younger female patients with abdominal pain, especially if accompanied by hormonal irregularities.

Keywords: Granulosa Cell Tumor • Granulosa Cell Tumor of the Ovary • Pediatrics • Sex Cord-Gonadal Stromal Tumors • Surgery Department, Hospital

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Background

Granulosa cell tumor (GCT) is a rare type of ovarian sex cord stromal tumor with an incidence of 0.4-1.7 per 100 000 women [1]. GCTs are divided into adult granulosa cell tumors (AGCT) and juvenile granulosa cell tumors (JGCT). GCTs account for 5-8% of all ovarian tumors, with only 5% of diagnosed GCTs being juvenile type [1-3]. JGCTs are usually found in the first 3 decades of life [3]. The median age at time of JGCT diagnosis is reported to be 8-17 years [3-5].

GCTs are derived from the granulosa cells of the ovary, which are the estradiol- and inhibin-secreting component of the ovary. Clinical manifestations of hyperestrogenism and excess secretion of inhibins in JGCT often present as symptoms of precocious puberty in younger females [2,3,6,7]. In adolescents and post-pubertal girls, these symptoms may present as menstrual irregularities, vaginal bleeding, and virilization, along with abdominal swelling and pain [2,3,6-8]. Menstruation-related clinical symptoms allow for an earlier noticeable presentation, which aids in earlier tumor detection, which may explain the fact that GCTs are detected as stage 1 80-90% of the time [9].

Here, we present a case of an obese 12-year-old girl with a unique presentation of JGCT arising from the left ovary that measured 15.0×9.0×18.8 cm, without the common symptoms of JGCTs such as precocious puberty and hyperestrogenism, but instead presented with secondary amenorrhea, hyperprolactinemia, and galactorrhea.

Case Report

A 12-year-old girl with childhood obesity, gallstones, and prediabetes presented to her primary care provider (PCP) with concerns of amenorrhea. She had menarche at 10 years of age but did not have regular menses for the past 2 years. Additionally, she had intermittent left lower abdominal pain for 2-3, months that was increasing in frequency in the days leading up to her visit. On physical examination, the patient was noted to have galactorrhea of both breasts. Further workup revealed elevated prolactin levels at 70.5 ng/mL (normal 4.8-23.3 ng/mL) in a setting of a total beta HCG level of <0.6 (normal 0.0-1.0 mIU/mL). The patient was subsequently given a working diagnosis of unspecified anterior pituitary hyperfunction.

An abdominal/pelvic ultrasound (US) was ordered by her PCP for further evaluation of the abdominal pain. The US showed an incidental large left-sided mass within the pelvis, with concerns for a possible neoplasm (**Figure 1**). Following these findings, the patient was seen in the Emergency Department (ED). Repeat pelvis US with Doppler was performed in the ED to evaluate for ovarian torsion, with redemonstration of the pelvic mass and no findings of ovarian torsion. She was admitted for further evaluation and management.

Computed tomography (CT) of the abdomen and pelvis with contrast showed a large, heterogeneously-enhancing, partially necrotic and cystic, solid abdominal/upper pelvic intraperitoneal mass measuring approximately 15.0×9.0×18.8 cm, appearing to arise from the left adnexa (**Figure 2**). The mass abutted the uterine fundus without invasion, and partially compressed the inferior vena cava and common iliac veins. The blood supply of the mass primarily came from a prominent left gonadal vessel appreciated intraoperatively.

The patient underwent an exploratory laparotomy and was found to have a large left ovarian mass originating from the left ovary, for which she underwent a left salpingo-oophorectomy. The mass was taken out en bloc as there was no identifiable ovary on the left side, but the right ovary was present. The resected mass weighed 1425 g and was limited to the ovary with no gross evidence of metastasis (**Figure 3**). No lesions were detected on the nearby liver, diaphragm, or omentum.

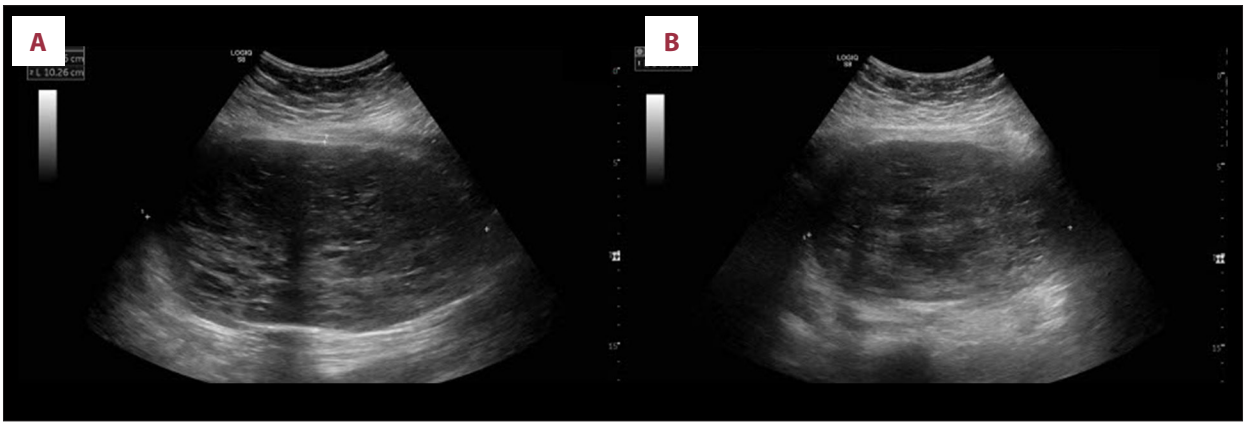

Figure 1. External transpelvic ultrasound of a heterogenous, predominantly solid pelvic mass. (**A**) Sagittal view of the mass. measuring 18.6×10.3 cm. (**B**) Transverse view of the mass, with its height measuring 14.4 cm.

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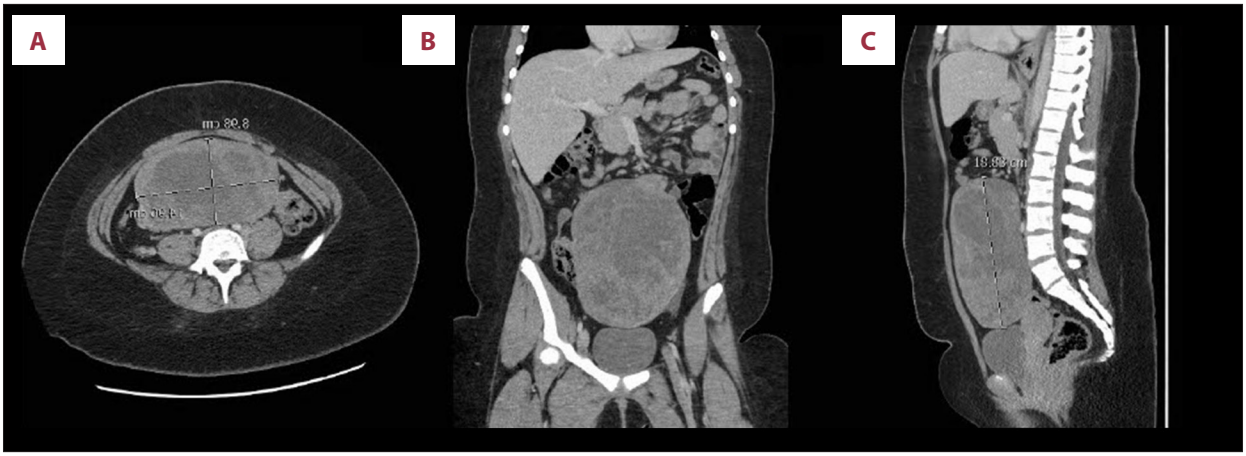

Figure 2. Computed tomography (CT) abdomen and pelvis with contrast. (**A**) Axial view of CT abdomen and pelvis of the juvenile granulosa cell tumor measuring 8.98×16.96 cm. (**B**) Coronal view of CT abdomen and pelvis of the juvenile granulosa cell tumor. (**C**) Sagittal view of CT abdomen and pelvis of the juvenile granulosa cell tumor with its height measured at 18.83 cm.

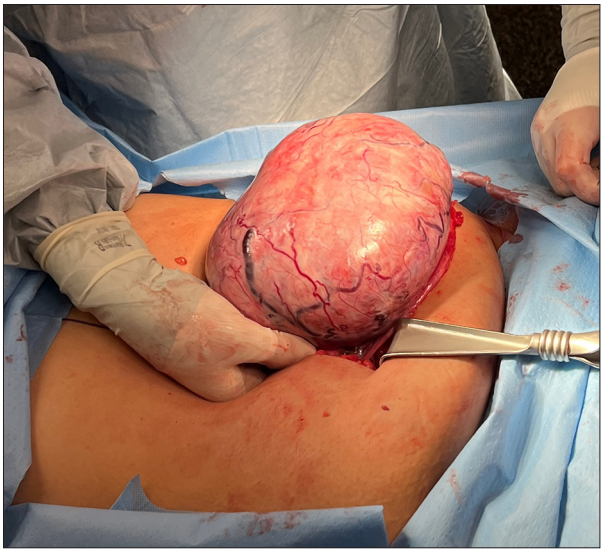

Figure 3. Intraoperative aspect of the left juvenile granulosa cell tumor.

Histopathological examination supported the diagnosis of granulosa cell tumor, juvenile type, Federation of Gynecology and Obstetrics (FIGO) stage 1A (**Figure 4**). The mass was confined to the ovary, with its capsule intact. No surface tumor was found on the ovary or fallopian tube, and no lymph-vascular invasion was identified. Immunohistochemical staining was positive for the antibodies inhibin and calretinin. No tumor was seen within a random omental biopsy, but focal reactive mesothelial cells were seen. No tumor cells were seen in the peritoneal washing samples.

The patient had an uneventful postoperative course and was discharged home in good condition on hospital day 4. She was seen in the clinic for follow-up 2 weeks postoperatively and was doing well without concerns.

Discussion

Our patient uniquely experienced galactorrhea and amenorrhea in the setting of elevated prolactin, which prompted additional workup along the hypothalamic-pituitary-adrenal axis, but it was not until our patient experienced abdominal pain that the workup included ultrasonography. The association of JGCT and galactorrhea in childhood is rare and has been underreported in the literature [10,11]. These non-specific signs and symptoms accompanying menstrual irregularities ultimately led to the diagnosis and treatment of JGCT. Despite the low incidence of JGCTs, the constellation of symptoms of amenorrhea, hormonal dysregulation, abdominal pain, and young age should always prompt investigation of ovarian etiologies.

JGCT has a higher incidence in young females. Usually benign, the prognosis is deemed to be excellent after salpingo-oophorectomy in patients who only have ovarian involvement [2] with low reoccurrence rates [6,8]. Clinically, JGCT is almost always symptomatic, often presenting with symptoms associated with hyperestrogenism, such as early breast development, increased pubic hair, and vaginal bleeding. In older patients, menstrual irregularities may be the main presenting symptom. Due to the location of GCTs, abdominal swelling, pain, and/or a palpable tumor in the lower abdomen may be important presenting signs/symptoms [3,6,9]. Tumor rupture is found in 10% of cases, which can present as acute onset of severe abdominal pain [3].

Differentiation of AGCT, JGCT, and other ovarian tumors is based on histological findings [1,3,6,12]. JGCT has a follicular pattern and is often positive for calretinin and inhibin on immunohistochemistry. However, negative inhibin does not rule out JGCT [7]. Presenting symptoms for JGCT are similar to other germ cell tumors and epithelial tumors, so it is important to distinguish between these entities for prognosis and future

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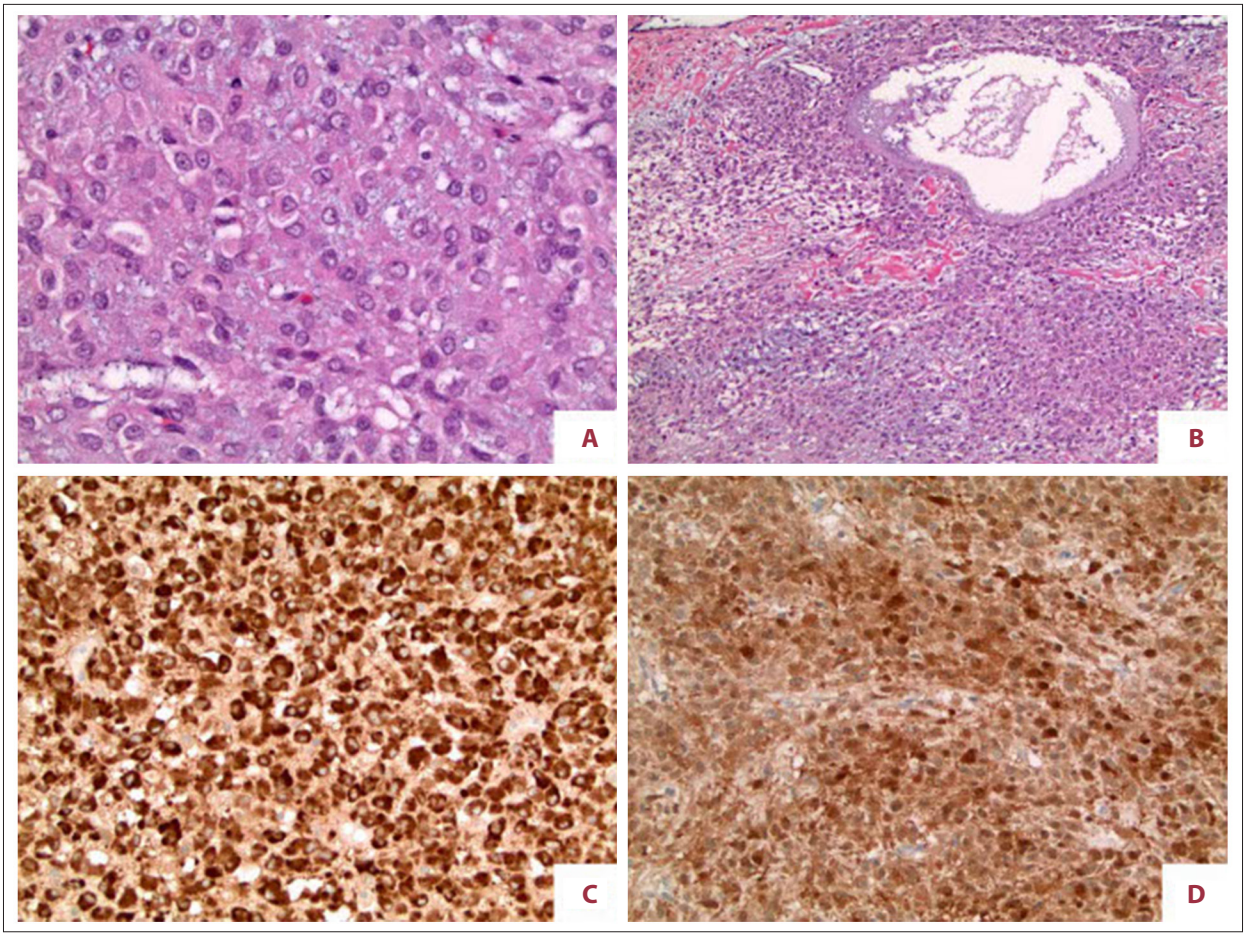

Figure 4. Photomicrographs of the diagnostic histopathology and immunohistochemistry of juvenile granulosa cell tumor of the ovary in a 12-year-old girl. (**A**) The histology of juvenile granulosa cell tumor shows cords of cohesive cells with eosinophilic cytoplasm and irregular cell nuclei, but no mitoses or necrosis. Hematoxylin and eosin (H&E). Magnification ×60. (**B**) Low-power histology of juvenile granulosa cell tumor shows sheets of tumor cells and some cystic areas. Hematoxylin and eosin (H&E). Magnification ×20. (**C**) Immunohistochemistry for calretinin shows positive brown staining of the cytoplasm of the tumor cells. Magnification ×40. (**D**) Immunohistochemistry for inhibin A shows positive brown staining of the nuclei of the tumor cells. Magnification ×60.

management [1]. Microscopically, nuclei of JGCTs are rounded, hyperchromatic, and ungrooved, with moderate eosinophilic or vacuolated cytoplasm and the theca cell component is luteinized, which are characteristics of JGCTs that distinguish them from AGCTs [13]. Additionally, staging of JGCTs uses the FIGO system. In stage I, the tumor is localized to the ovary or fallopian tube; stage II tumor involves both the ovary and fallopian tube or has locally invaded nearby structures such as the bladder; stage III tumor have spread to local lymph nodes or invaded the peritoneum; and stage IV is metastatic disease [14].

For this patient, the JGCT was confined to the ovary alone, meeting the criteria for stage I disease. For patients of reproductive age, fertility preservation should be considered for the patient's quality of life. In patients with stage 1 disease, conservative unilateral salpingo-oophorectomy is indicated [3]. Stage I JCGTs have a 5-year survival rate of 90-95%, with low reoccurrence [8]. However, GCTs can recur 20-30 years following initial treatment; thus, a protracted monitoring period is necessary [8,14]. Prognostic factors include tumor stage and size, increases in body mass index, and failure to resect the tumor en bloc [6,9].

Another case report, by Larizza et al, presented a patient with JGCT without precocious puberty but with secondary amenorrhea and hyperprolactinemia with no evidence of hypothalamic pituitary abnormalities, which was similar to our patient's unusual presentation of JGCT[15]. Larizza et al suggested that the tumor may have been present during the patient's 4-year history of amenorrhea after her spontaneous menarche. Our patient had a 2-year history of amenorrhea after menarche, so it may be reasonable to think that the tumor had been growing for 2 years.

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A case report by Ashnagar et al discussed differing clinical symptoms of JGCT, in which a 13-year-old girl had massive ascites and primary amenorrhea as the primary presenting symptoms of JGCT stage 1C [1]. She was negative for other clinical evidence of precocious pseudopuberty. The patient had increased levels of serum inhibin, blocking FSH, which was proposed as the possible causative agent of the patient's primary amenorrhea. The patient underwent tumor resection with left salpingo-oophorectomy and omentectomy. She developed menarche 10 days after surgery. This case shows that the hormonal symptoms related to the JGCT will resolve after removal of the tumor.

Conclusions

This case of a JGCT found in a 12-year-old pre-pubertal obese girl is uncommon, largely due to the rarity of JGCTs, along with her absence of common clinical precocious pubertal or hyperestrogenic symptoms. The secondary amenorrhea, which is considered a common presentation of JGCT in adolescents, was initially assumed to be normal for the patient's developmental age. This case presentation underscores the low threshold primary care providers should have to initiate a workup for ovarian tumors, even in the setting of typical-for-age symptoms. Missed ovarian tumors can have long-term effects on the development of the child and prognosis once the tumor is identified.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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