Case Report

Juvenile granulosa cell tumor of the ovary: A rare cause of precocious puberty in a toddler

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ABSTRACT

Ovarian tumors are a rare cause of sexual precocity in female children. Functional neoplasms of the ovary are relatively infrequent, and only 5% occur before puberty. Although ovarian juvenile granulosa cell tumor (GCT) is a rare tumor described infrequently in pediatrics, the most common presentation of this tumor is precocious puberty. We report a 1½ year-old girl with isosexual precocious puberty, who presented with a rapid onset of premature menarche, pubic hair, and vaginal bleeding, with an abdominal mass on clinical examination. Ultrasonography of the pelvis and abdomen showed a heterogeneously hypoechoic solid mass with cystic areas and internal vascularity. The child underwent a left oophorectomy. Microscopic features of the resected mass were characteristic of juvenile GCTs. Even though the most common cause of precocious puberty in girls is idiopathic, functional ovarian tumors must be considered, especially when the onset is at an early age and puberty is rapidly progressive. Early-stage disease has a good prognosis, and adjuvant chemotherapy is not indicated.

Key words: Juvenile granulosa cell tumor, Ovary, Precocious puberty

Granulosa cell tumor (GCT) is a rare type of ovarian sex cord-stromal tumor with an incidence of 0.4–1.7/1,00,000 women [1]. It was first described by Rokintasky in 1855 [2]. The two types of GCTs are adult GCT and juvenile GCT. Only 0.1% of all ovarian tumors and 4–5% of GCT occur in children [3]. GCT accounts for 5–8% of ovarian tumors, with only 5% of diagnosed GCTs being juvenile type [3]. GCTs are derived from the granulosa cells of the ovary, which are the estradiol and inhibin-secreting component of the ovary and are the second-most common source of autonomous ovarian estrogen after functional ovarian cyst [4]. Precocious puberty is defined as the onset of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys. Although isosexual precocious puberty in a girl is most commonly idiopathic in origin, it is a diagnosis of exclusion, and differential diagnoses must be thought of in the evaluation. Estrogen-secreting tumors must be considered in the differential diagnosis of precocious puberty in girls, even though it is rare.

We report a case of isosexual precocious puberty in a $1\frac{1}{2}$ year-old girl with juvenile GCT of the ovary, a rare etiology of precocity.

CASE REPORT

A $1\frac{1}{2}$ year-old girl child, the first child of non-consanguineous parentage with no previous significant history, was brought with complaints of breast enlargement and the appearance of pubic hair noticed by the mother for 2 weeks and bleeding per vagina for 2 days. There was the maintenance of the harmony of normal puberty, that is, breast and pubic hair development, followed by menarche.

Physical examination revealed her height at the 25th centile and weight at the 50th centile. Her pulse rate was 108/min, respiratory rate was 28/min, and blood pressure was 84/50 mmHg with no dysmorphism, bony deformities, or café-au-lait macules, Tanner stage II breast, and pubic hair development. Her bone age, height age, and chronological age were 22 months, 20 months (88 cm), and 18 months respectively. Abdominal examination revealed a mobile, non-tender, firm mass of 8×5 cm in the left lower abdomen. She had normal blood counts and liver, renal, and thyroid function tests.

Her serum laboratory findings were consistent with peripheral precocious puberty. The serum estradiol was elevated at 351 pg/mL (<10 pg/mL) with a suppressed luteinizing hormone (LH)-0.01 mIU/mL (<0.3 mIU/L) and follicle-stimulating hormone (FSH)-0.49 mIU/mL (4 mIU/L) levels.

Abdominopelvic ultrasonogram showed a heterogeneously hyperechoic solid lesion with cystic areas and internal vascularity in the pelvis, possibly left ovarian origin measuring 8×4×7.2 cm with no calcification. The uterus was mildly bulky with thickened endometrium (6 mm) and a normal right ovary. Tumor markers, including inhibin A, beta-human chorionic gonadotropin (hCG), and alpha-fetoprotein (AFP), were done. Inhibin A was

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elevated-790 pg/mL (<7 pg/mL); however, hCG and AFP were normal. Diagnosis of isosexual precocious pseudo puberty due to estrogen-secreting ovarian tumor was made.

She was taken up for laparotomy on the 5th day of admission by the pediatric surgeon. The intraoperative findings were uniformly enlarged left ovary with a solid tumor of the size of 7×6×4 cm and freely mobile with no separate ovarian tissue. The peritoneum contained 10–15 mL of serous fluid, and the sample was taken for cytology, which came negative for malignant cells. The left fallopian tube, right ovary, and the right fallopian tube were normal. The liver and spleen were normal, and the para-aortic and mesenteric lymph nodes were not enlarged. A left oophorectomy with surgical staging and peritoneal washings was performed by the pediatric surgeon. Grossly, the tumor was well-encapsulated, the surface showed congested blood vessels, and the cut surface identified solid and cystic areas predominantly solid, gray-white lobulated with specs of hemorrhage, and cystic areas were trabeculated to let out pale yellow serous fluid (Fig. 1).

Histopathological examination revealed focal macrofollicular, microcystic, cords, and pseudopapillary pattern, and individual cells are polygonal with scant eosinophilic to clear cytoplasm, pleomorphic vesicular nuclei with prominent nucleoli and no nuclear grooving, and 7–9 mitotic figures/hpf (Fig. 2). Immunohistochemistry revealed tumor cells are positive for Inhibin A (Fig. 3). A final diagnosis of benign juvenile granulosa cell ovarian tumor Stage 1 A, according to the International Federation of Gynecology and Obstetrics (FIGO stage 1A), was made.

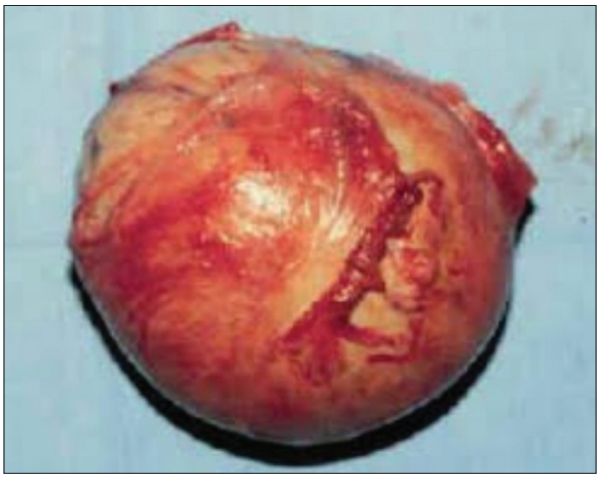

Figure 1: Goss specimen of ovarian tumor

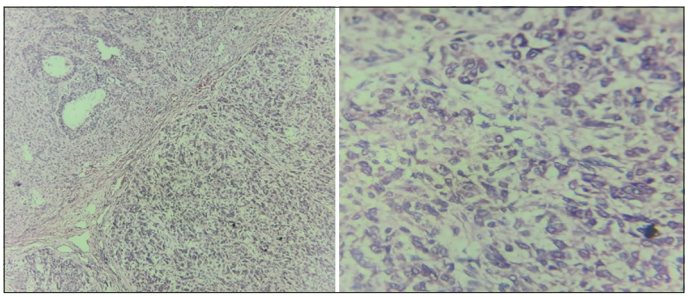

Figure 2: (a) Low-power and (b) high-power microscopy showing tumor cells (H and E staining)

The postoperative course was uneventful, and her breast size and pubic hair regressed, menstrual bleeding stopped, and serum estradiol levels came down to normal. Even after 30 months, she has not developed any signs of recurrence.

DISCUSSION

Peripheral precocious puberty or gonadotropin-independent precocious puberty or precocious pseudo puberty constitutes <20% of cases of precocious puberty in girl children [2,3]. The causes of isosexual peripheral precocity in girls include functional ovarian follicular cysts, estrogen-secreting ovarian or adrenal tumors, environmental exposure to compounds with estrogenic activity, severe untreated primary hypothyroidism, and McCune–Albright syndrome. Of these, functional ovarian follicular cysts are the most frequent cause followed by estrogen-secreting ovarian tumors [3,4].

Ovarian tumors account for approximately 1% of all tumors in children and adolescents and are rare causes of precocity. Epithelial tumors (70%), germ cell tumors (20%), and sex cord-stromal tumors (8%) are the three main types. Ovarian sex cord-stromal tumors are neoplasms containing granulosa cells, Sertoli cells, theca cells, Leydig cells, and fibroblasts of gonadal stromal origin. GCT represents about 2% of all ovarian tumors and is a type of ovarian sex cord-stromal tumor. GCTs are classified into adult (95%) and juvenile (5%) types based on their histology and age of onset. Juvenile GCT of the ovary makes up <5% of childhood ovarian tumors and is usually manifested in the first three decades of life. Even though isosexual precocity occurs in 70–80% of prepubertal girls with GCTs, only 1% of all cases of sexual precocity in prepubertal girls are due to GCTs.

The clinical significance of GCT is due to its estrogen-secreting property resulting in pseudo-precocity since ovulation does not occur. Approximately, 82% of prepubertal girls presented with symptoms of precocious puberty, including the appearance of pubic hair, breast enlargement, vaginal bleeding, and advanced bone age as seen in our child [2,3,5]. In addition to precocious puberty, abdominal mass can be another presentation. Our child did not present with an abdominal mass; however, it was picked up in the clinical examination. Although the historic classical triad described as a palpable adnexal

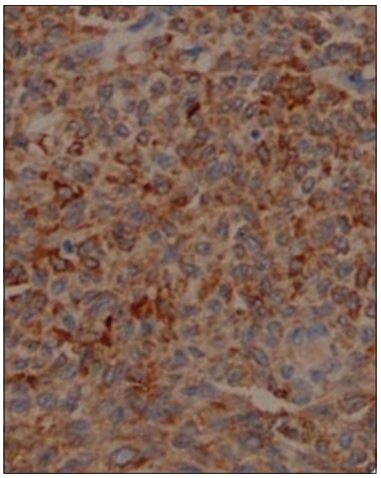

Figure 3: Immunohistochemical satin-inhibin positive tumor cells

mass, raised serum estradiol, and absent or decreased gonadotropins is reported to be almost diagnostic of GCT, there are diverse reported presentations, including virilization, massive ascites, pleural effusion, primary amenorrhea, acute abdomen due to torsion/rupture, and Meigs syndrome [5]. The presence of undetectable basal serum FSH and LH levels had a specificity of 95% in girls with gonadotropin-independent precocious pseudo-puberty [6]. There will be high levels of sex hormones and suppressed gonadotropins as in our case. Juvenile GCT has also been associated with various congenital anomalies, including Ollier disease, Maffucci syndrome, leprechaunism, Potter syndrome, hypercalcemia, Peutz–Jeghers syndrome, and cytogenetic aberrations.

The most specific markers are inhibin and anti-Mullerian hormone, followed by estradiol levels. After surgery, a follow-up with inhibin or AMH is recommended. Hormone levels, most commonly serum inhibin concentration, should return to normal postoperatively and can be used to assess response to treatment and monitor for recurrence and spread. Tumor markers such as AFP, β-hCG, CA 125, CEA, and CA 19.9 could indicate the presence of ovarian malignancy. Tumor markers, whether positive or negative, are not conclusive in all cases, but are useful for postoperative surveillance [5-7].

Ultrasound is the imaging modality of choice in cases of ovarian masses in children, particularly for the initial workup. The presence of more solid components in the tumor is a definite feature that predicts malignancy. Computed tomography (CT) scan and magnetic resonance imaging are useful in cases of undefined mass if malignancy is suspected or can be done before surgery because they give additional information about the nature of the tumor and the presence of pelvic and para-aortic lymph nodes and, therefore, increase the accuracy of the diagnosis of ovarian malignancy. Sonographically, GCTs are usually solid and cystic or mainly solid with a spongiform appearance, with the solid portion being heterogenous in echogenicity as seen in our child. There can be associated uterine enlargement and endometrial thickening due to estrogenic action on the endometrium, which was present in our child. Being a functional ovarian tumor, patients with juvenile GCT demonstrate elevated serum levels of estradiol and inhibin as was noted in our child. GCTs are usually capsulated with solid or cystic components, and extracapsular invasion is rare as described in our child. Neoplastic cells have ample eosinophilic cytoplasm, polymorphic nuclei, and mitotic figures. A positive immunohistochemical stain for inhibin is also diagnostic, which is positive in our child.

According to the FIGO system, the tumor staging was FIGO stage 1 in our child. Literature studies also show that most tumors are unilateral and FIGO stage 1 [8,9]. Surgery is the primary standard initial treatment. Unilateral salpingo-oophorectomy is the treatment of choice in children and women of reproductive age with stage 1 disease. Diagnosis at stage 1 has a favorable prognosis. A worse prognosis and early recurrence should be expected in advanced disease [9,10]. Adjuvant chemotherapy with a cisplatin-based regimen is needed if the tumor is FIGO stage I c and III c or has a high mitotic rate.

Juvenile GCTs have excellent cure rates. The 5-year survival rates are 90–95% for FIGO stage I tumors and 25–50% in the advanced stage. Age <10 years, presence of precocious puberty, and FIGO stage 1 tumor are associated with a good prognosis [2]. Close follow-up is needed since recurrences occur especially during the first 3 years after diagnosis. Although Stage I juvenile GCTs are less likely to recur after surgery, late recurrences can occur even in Stage I patients, necessitating long-term follow-up. Our child is under follow-up for 30 months and is so far free of recurrence.

CONCLUSION

Our case illustrates a rare cause of precocious puberty in a girl child – a juvenile GCT of the ovary. Although ovarian estrogen-secreting tumors are a rare etiology in precocious puberty, the most common presentation of GCT of the ovary in children is precocious puberty. Timely diagnosis and complete surgical excision of the tumor lead to the normalization of hormone levels and regression of secondary sexual characteristics. There is an excellent prognosis for the early stage. Because most of these lesions are benign, ovarian-preserving operations should be performed whenever feasible. Ovarian masses, although rare in children, must be included in the differential diagnosis of all girls who present with precocious puberty.

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