Case Report

Juvenile Granulosa and Theca Cell Tumor of the Ovary as a Rare Cause of Precocious Puberty: Case Report and Review of Literature

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Abstract. Background: The differential diagnosis for precocious puberty in a young female includes peripheral causes. This case documents a rare cause of peripheral precocious puberty—a juvenile granulosa and theca cell ovarian tumor—and a brief review of the literature for this tumor type.

Case: A 7-year-old girl presented with rapid onset of pubertal development and elevated estradiol levels. Menarche occurred 5 months after thelarche. A thorough workup revealed a large multicystic left ovary. Other causes of precocious puberty were excluded. She underwent an exploratory laparotomy and left salpingo-oophorectomy. Pathology reported a juvenile granulosa and theca cell tumor of the ovary, FIGO stage 1A. Postoperatively, she experienced a cessation of vaginal bleeding and estradiol levels normalized. A literature review found that early stage disease has an excellent prognosis and that adjuvant chemotherapy is not indicated in this setting.

Summary and Conclusion: Juvenile granulosa and theca cell tumor of the ovary is a rare cause of peripheral precocious puberty, even more so than juvenile granulosa cell tumors. Premenarchal granulosa-theca cell tumor (GTCT) is an even rarer entity.1 We report a rare case of a juvenile granulosa and theca cell ovarian tumor associated with isosexual precocious puberty in a 7-year-old female and review the available literature associated with this condition.

Introduction

Although the etiology of most cases of precocious puberty in young females is idiopathic, this is a diagnosis of exclusion and many disorders need to be considered in the evaluation of a young female with early isosexual development. In cases of peripheral (gonadotropin independent) precocious puberty, a tumor or cyst of ovarian or adrenal origin produces estrogen autonomously. Approximately 60% of ovarian tumors that cause sexual precocity are granulosa cell tumors. Premenarchal granulosa-theca cell tumor (GTCT) is an even rarer entity.1 We report a rare case of a juvenile granulosa and theca cell ovarian tumor associated with isosexual precocious puberty in a 7-year-old female and review the available literature associated with this condition.

Case

A 7 year 1 month old girl presented with a 10-day history of vaginal bleeding. This had been preceded by 5 months of breast development and accelerated growth followed by pubarche. Her review of systems was unremarkable. There was no history of vaginal foreign body or inappropriate sexual contact. Her previous medical history and birth history were unremarkable. She was on no medications. There was no family history of endocrinological disorders or precocious puberty.

On examination, her weight was 31.7 kg (90th percentile) and height was 137 cm (> 95th percentile); this represented an acceleration in her height velocity from the 50th percentile. Vital signs were normal. She had normal ocular, thyroid, and cardiorespiratory examinations and no lymphadenopathy. She had no café-au-lait spots but was noted to have a 2-cm pigmented lesion located subcostally along the right mid-axillary line. No acne or hirsutism was noted. She was Tanner stage III for breast development and Tanner II for pubic hair. Her abdomen was non-tender with but there was a palpable fullness in the lower quadrants. There was no obvious ascites.
She had a crescentic hymen and marked estrogenization of the vulva and vagina but no active bleeding. The anus appeared normal.

Multiple investigations were undertaken to determine the etiology of her precocious puberty (Tables 1 and 2).

A pelvic ultrasound revealed a fluid-filled multicystic left ovarian cyst measuring $13.0 \times 6.4 \times 8.1$ cm. Thin septa were seen and the cystic spaces were anechoic with very little appreciable solid tissue. The right ovary measured $2.2 \times 1.2 \times 1.6$ cm and contained small follicles. The uterus was enlarged with a length of $3.4$ cm (normal $\leq 3$ cm) and had an increased endometrial thickness of $1.5$ cm. There was no evidence of ascites (Fig. 1).

A pelvic-abdominal CT scan confirmed a multicystic left ovarian cyst. No other abdominal or pelvic abnormalities were seen and there was no evidence of lymphadenopathy.

At a chronological age of 7 years 6 months, her bone age was advanced to 10 years (SD 8.3 months). Laboratory investigations revealed an elevated estradiol (668 pmol/L, normal $< 20$ pmol/L) and suppressed baseline FSH and LH ($< 1$ IU/L). A bone scan was normal. The latter was performed to exclude an atypical case of McCune-Albright syndrome. Electrolytes, CBC, liver function tests, and serum TSH were normal. Her androgens were also normal.

Table 1. Diagnoses Eliminated in Investigations of Precocious Puberty and Ovarian Mass

<table>
<thead>
<tr>
<th>Test Performed</th>
<th>Result</th>
<th>Diagnosis Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>Normal</td>
<td>Thyroid abnormality</td>
</tr>
<tr>
<td>Bone scan</td>
<td>Normal</td>
<td>McCune-Albright syndrome</td>
</tr>
<tr>
<td>Androgens</td>
<td></td>
<td>Androgen-secreting tumor</td>
</tr>
<tr>
<td>DHEAS</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Free testosterone</td>
<td>Negave</td>
<td>Choriocarcinoma, embryonal carcinoma, polyembryoma, serous or mucinous tumor, endodermal sinus tumor, mixed germ cell tumor, dysgerminoma</td>
</tr>
</tbody>
</table>

Table 2. Investigations for Causes of Precocious Puberty

<table>
<thead>
<tr>
<th>Test Performed</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>Elevated</td>
</tr>
<tr>
<td>LH, FSH</td>
<td>$&lt; 1$</td>
</tr>
<tr>
<td>Bone age</td>
<td>Advanced</td>
</tr>
<tr>
<td>Pelvic ultrasound</td>
<td>Fluid-filled multicystic left ovarian cyst with thin septae ($13.0 \times 6.4 \times 8.1$ cm). Enlarged uterus, increased endometrial thickness. No ascites</td>
</tr>
<tr>
<td>Pelvic-abdominal CT scan</td>
<td>Multicystic left ovarian cyst; did not provide additional information</td>
</tr>
<tr>
<td>CA-125</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

(DHEAS 0.7 μmol/L, free testosterone $< 0.5$ pmol/L). All tumor markers, including βHCG, CEA, AFP, LDH, and ALP, were negative, with the exception of CA-125 which was elevated at 55 u/ml (normal 0–35 u/ml). Inhibin levels were not measured because testing was not readily available in our center.

She failed a trial of medroxyprogesterone acetate to stop the vaginal bleeding until her evaluation was completed. She became symptomatic with pelvic pressure, early satiety, urgency, and enuresis and was consented for surgery.

She underwent exploratory laparotomy, pelvic washings, and left salpingo-oophorectomy as we suspected an ovarian tumor. On inspection, the left ovary measured $15 \times 7$ cm and had a smooth surface with no excrescences or papillary projections. The left tube was elongated along the course of the distended ovary (Fig. 2). The uterus was small but pubertal in shape. The right ovary was small with no evidence of cysts. The right fallopian tube was normal. There was no evidence of ascites or peritoneal deposits and the surfaces of the bowel, liver, and omentum were normal. No pelvic or para-aortic nodal enlargement was seen.

The final pathology was a partially luteinized juvenile granulosa and theca cell tumor with an intact capsule (FIGO 1A). On gross examination, the ovary measured $14 \times 7.5 \times 6.5$ cm and there were no surface excrescences or nodules. The cyst itself was multiloculated and contained clear, watery serous-type fluid. The septa contained small yellowish nodules ranging from 1 to 5 mm in diameter. On microscopic examination, the tumor was predominantly cystic and consisted of partially luteinized proliferating granulosa cells. In some areas, there was variable proliferation of theca cells with and without luteinization. The predominant pattern was granulosa cell proliferation (Fig. 3) with many Call-Exner bodies present (Fig. 4). Nuclear grooving was
rare. There was mild mitotic activity with no bizarre nuclei. The ovarian capsule was intact and there was no extension of the tumor cells into the adjacent fallopian tube. The immunohistochemistry showed that the granulosa cells were reactive with Keratin 18, Vimentin, and CD99 but non-reactive with EMA and S100. This staining pattern confirmed the dual epithelial/mesenchymal differentiation of neoplastic cells and was characteristic for granulosa cells.

Her postoperative course was unremarkable and cessation of vaginal bleeding occurred within 2 weeks of surgery. Estradiol decreased to 6.1 pmol/L, CA-125 11 u/ml (normal) and LH and FSH were <1 IU/L. Her follow-up consisted of clinical assessments (history/physical), laboratory investigations (estradiol, CA-125) and imaging (ultrasound alternating with CT abdomen/pelvis). She has been followed every 3 months for 2 years, then every 6 months. At one-year follow-up, her height remained at the 95th percentile, breast development had regressed to Tanner stage II, estradiol in prepubertal range 32 pmol/L and CA-125 at 9 u/ml (normal). At 2-year and 3-year follow-ups, her height remained at the 95th percentile, breast development had fully regressed to Tanner I, estradiol <18 pmol/L and CA-125 is 10 u/ml (normal). She remains tumor free clinically and radiographically at 4 years. The oncology team plans to continue follow-up for a total of 10 years.

Summary

Malignant ovarian tumors are rare in children\textsuperscript{2} and represent only 1\% of all pediatric malignant tumors.\textsuperscript{3} Most of these are germ cell tumors.\textsuperscript{4,5} Granulosa cell tumors (GCT) are divided into juvenile GCT and adult GCT based on clinical presentation and histology. Less than 5\% of all ovarian GCTs occur prepubertally.\textsuperscript{3,6} In 70—90\% of cases, GCTs in the young female present with isosexual precocity.\textsuperscript{3,7,8} Compared to juvenile GCT, only 1\% of all cases of sexual precocity in prepubertal girls are due to granulosa-theca cell tumors, an even rarer entity due to the theca component.\textsuperscript{7} The triad of a palpable adnexal mass, elevated serum estradiol levels, and absent or decreased gonadotropins (FSH and LH) have been reported to be almost diagnostic of a GTCT in a premenarchal girl.\textsuperscript{1} However, not all cases of GTCT will present with these findings, leading to a possible delay in diagnosis.

Rapid onset of precocious puberty is indicative of an ovarian tumor.\textsuperscript{7} Indeed, clinical suspicion, hormonal investigations, tumor markers, and imaging will result in correct diagnosis in most circumstances. Clinical manifestations of an ovarian GTCT may also include abdominal swelling, pain, or a palpable mass. In 10\% of cases of juvenile GCT, the tumor may rupture and present with acute abdominal pain and...
hemoperitoneum. Serum estradiol, CA-125, and inhibin may be related to tumor burden and chemotherapy response. In a retrospective review of 40 cases of ovarian juvenile granulosa cell tumors, Plantaz et al found the first signs and symptoms were abdominal pain (52%) and endocrine symptoms (48%). At diagnosis, 94% had abdominal signs such as increased abdominal girth and palpable tumor. Sixty-eight percent had endocrine signs of precocious puberty. All girls diagnosed on the basis of precocious puberty were FIGO stage 1A.

Juvenile GTCTs secrete estradiol due to the presence of theca cells that secrete androstenedione which is subsequently converted to estradiol by the granulosa cells. Serum estradiol is thus usually elevated at the time of diagnosis. Although some have advocated using estradiol levels to follow these patients, the use of estradiol levels to monitor the course of disease for GCT in adults is controversial. Inhibin, which is synthesized by the granulosa cells, may be related to tumor burden and chemotherapy response. Serum FSH and LH are very low. In one case of a juvenile GCT with early pseudopuberty, alphafetoprotein levels were elevated. In our case, all tumor markers were negative but the CA-125 was elevated. Although CA-125 is a sensitive marker for epithelial ovarian tumors, it is not very specific and may be elevated in other intraperitoneal processes. Our patient presented with a multicystic unilateral ovarian mass, a small pigmented lesion and precocious puberty. Consequently, a bone scan was performed to exclude an atypical presentation of McCune-Albright syndrome.

The primary treatment of juvenile GCT and GTCT is surgical. The extent of surgery must be carefully evaluated to preserve fertility and hormone function and unilateral oophorectomy is the first choice for treatment; there is no role for simple ovarian cystectomy. Staging should include peritoneal cytology, exploratory laparotomy, and unilateral salpingo-oophorectomy. For more extensive disease, staging operation should include unilateral oophorectomy or salpingo-oophorectomy, total omentectomy, resection of any metastatic lesions from the peritoneal surfaces, pelvic and paraaortic lymphadenectomy, and peritoneal cytology. Bilateral ovarian involvement is uncommon in stage 1A tumors and wedge biopsy is not recommended if the contralateral ovary appears grossly normal. Prognostic factors include the stage of the tumor, the size of the tumor, the degree of nuclear atypia, and mitotic activity. Tumor rupture does not appear to be a negative prognostic factor. Chemotherapy is not required in patients with stage 1A tumors, nor does it appear to be indicated for tumors that have been complicated by rupture. Expert pathologic review is recommended to ensure the correct diagnosis of this rarely encountered neoplasm. Treatment for more disseminated, metastatic, or recurrence of tumors that are Stage 1C or higher is more difficult. Optimal adjuvant treatment is not known. Serum estradiol, CA-125, and inhibin may be used for follow-up postoperatively.

The biologic behavior of juvenile GTCT may be less aggressive than histology would predict. Due to limited long-term follow-up data in the literature at the time, Lack et al urged further reporting of juvenile GTCT with follow-up times in order to see if they have a more favorable prognosis than adult tumors. Fortunately, prognosis and outcome for juvenile GCT and GTCT are good in most cases. It is a hormonally active tumor, thus diagnosis can be made quickly in early stage disease. In Cronje’s tumor registry review, precocious puberty subsided and physiologic puberty occurred at the normal expected age in all cases after tumor removal. The most favorable prognostic factor for juvenile GCT is early stage disease. Survival for Stage 1 is 78%–92%, while for Stage 1A it is 83%–98%. Kalfa et al reviewed 40 pre- and post-pubertal girls who had an ovarian GCT, of whom 17 were diagnosed on the basis of peripheral precocious puberty. All of the girls who were diagnosed with juvenile GCT on the basis of peripheral precocious puberty were FIGO IA (100%) with no evidence of peritoneal spread. They also found that a delayed diagnosis of juvenile GCT in the 11 girls who presented initially with endocrine signs was associated with peritoneal spreading of the tumor (72% FIGO IC or IIC vs. 10% with early diagnosis) and had a high risk of recurrence. Despite this, the prognosis was good with 82% disease-free and 97% survival at 4.5 years. Most juvenile GCT recurrences occur in the first year after initial diagnosis, but may be as late as 4 years. Recurrence is usually rapid, leading to death within 13 to 16 months. Close surveillance may be warranted for a longer duration.

There does not appear to be a consensus on appropriate postoperative assessments and follow-up in the literature. The follow-up of our patient consisted of clinical assessments (history/physical), laboratory investigations (estradiol, CA-125) and pelvic-abdominal imaging. She has been followed every 3 months for 2 years, then every 6 months. She remains tumor free clinically or radiographically at 4 years. The oncology team plans to continue follow-up for a total of 10 years.

In conclusion, juvenile granulosa and theca cell tumor of the ovary is a very rare cause of peripheral precocious puberty. The treatment of choice is surgery which is necessary for histological diagnosis, staging, and debulking. An excellent prognosis is possible in an early stage disease.
References
