

# Case Report with Review of Literature

## Juvenile granulosa cell tumor presenting as isosexual precocious puberty: A case report and review of literature

Nisha Nigil Haroon, Gaurav Agarwal<sup>1</sup>, Rakesh Pandey<sup>2</sup>, Preeti Dabadghao<sup>3</sup>

Department of Endocrinology, UHN Toronto General Hospital, Toronto, Canada, Departments of <sup>1</sup>Endocrine Surgery, <sup>2</sup>Pathology and <sup>3</sup>Endocrinology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

### ABSTRACT

The differential diagnosis for precocious puberty in a young female includes peripheral causes. This case report documents a rare cause of isosexual precocious puberty, a juvenile granulosa cell tumor of the ovary—and a brief literature review. A 7-year-old girl presented with rapid onset of pubertal development and elevated estradiol levels. Abdominal ultrasound revealed a mass in the right adnexa. Other causes of precocious puberty were excluded. Elective surgery was planned, but the patient presented to the emergency room with torsion of ovary. She underwent an exploratory laparotomy for tumor resection and right salpingo oophorectomy. Pathology reported a juvenile granulosa cell tumor of the ovary. Postoperatively, she experienced a cessation of vaginal bleeding and estradiol levels normalized. Early stage disease has good prognosis. Adjuvant chemotherapy is not indicated in this setting.

**Key words:** Juvenile granulosa cell tumor, precocious puberty, ovarian tumour, paediatric endocrinology

### INTRODUCTION

Isosexual precocious puberty in girls is mostly idiopathic in origin. But, this is a diagnosis of exclusion, and many differential diagnoses have to be thought of in evaluation of precocity in girls. We report a case of isosexual precocity in a 7-year-old girl due to juvenile granulosa cell tumor (GCT) of ovary (JGCTO), a rare etiology of precocity.

### CASE REPORT

A 7-year-old girl presented with 18 months history of progressive breast development. She had attained menarche 1 year back and had bled 3-4 times. There was no evidence

of local trauma or sexual abuse. Mother noticed hair growth over pubic area for 3-4 months and accelerated growth for 6 months. There was no history of meningitis, cranial irradiation, head trauma, headache, vomiting, gelastic seizures, medication intake, hypothyroidism, or systemic illness. Antenatal, perinatal, and developmental history was unremarkable. Her height (125.2 cms) and weight (26 kilograms) were above the 75<sup>th</sup> centile for age.<sup>[1]</sup> Vital signs were normal. She was Tanner stage IV for breast development and Tanner III for pubic hair. There were no bony deformities, *café-au-lait* spots, or signs of virilization. Systemic examination was normal. Her abdomen was soft, non-tender with no obvious mass palpable or ascites. She was investigated to determine the cause for precocity. She had normal blood counts, liver function tests, kidney function tests, and TSH level. Serum estradiol level was elevated (414 pg/ml, prepubertal <20 pg/ml) with a suppressed FSH level (<1 IU/L). At a chronological age of 7 years 2 months, her bone age was advanced to 8 ½ years. A pelvic ultrasonographic scan showed a well-defined heterogeneous solid mass lesion in the right adnexa measuring 6 × 7 × 9 cms. There were few hypochoic areas suggestive of necrosis. There was

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10.4103/2230-8210.107870

**Corresponding Author:** Dr. Preeti Dabadghao, Department of Endocrinology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow - 226 014, India E-mail: preetid@sgpgi.ac.in

increased perilesional and intralesional vascularity. Right ovary could not be seen separately from the mass. Left ovary was normal. Uterus, measured 6 × 2 × 2 cms, was anteverted and had an endometrial thickness of 3.4 mm. Tumor markers including beta-HCG, CEA, and AFP were negative. Inhibin levels were not measured as testing is not easily available at our center. A diagnosis of isosexual precocity due to estrogen-secreting ovarian tumor was made. Elective excision of the mass was planned. But, a week later, she presented to the emergency department with abdominal pain necessitating emergency laparotomy. The right ovary was enlarged and twisted on its pedicle, and right salpingo oophorectomy was done. The resected tumor was encapsulated without any capsular breach, measured 450 grams and had 10 × 8 × 5 cms dimension. The left ovary was normal. There was no fluid in the cul-de-sac and no lymphadenopathy. Histologic examination revealed micro follicular and nodular patterns of tumor cells with round to oval nuclei, nuclear grooving, inconspicuous nucleoli, moderate cytoplasm, and extensive luteinisation. Fallopian tube was tumor-free. Ascitic fluid was negative for malignant cells. A final diagnosis of a benign feminizing JGCTO (FIGO Stage IA) was established.

Postoperative course was uneventful, and her breast size regressed, menstrual bleeding stopped, and serum estradiol levels came down to normal. Even after 3 and half years, she has not developed any signs of recurrence.

## DISCUSSION

Peripheral or gonadotropin independent precocity constitutes less than 20% of precocity cases.<sup>[2]</sup> Causes of isosexual peripheral precocity in girls include ovarian follicular cyst, estrogen-secreting adrenal or ovarian tumors (GCT, sex-cord tumor, and estrogenizing Sertoli-Leydig cell tumors), and environmental exposure to compounds with estrogenic activity, severe untreated primary hypothyroidism, and McCune–Albright syndrome. Functional ovarian follicular cysts are the most frequent cause.<sup>[2]</sup>

Ovarian tumors are uncommon during childhood and are rare causes of precocity. Epithelial cell tumors (>70%), germ cell tumors (20%), and sex cord–stromal tumors (8%) are the 3 main types. Granulosa cell tumors (GCTs) represent about 2% of all ovarian tumors and fall under ovarian sex cord–stromal tumors. GCTs are classified into adult and juvenile types. JGCTOs make up less than 5% of childhood ovarian tumors and usually present in the first 3 decades of life. The most frequent presentation in prepubertal girls is precocity.<sup>[3,4]</sup> Clinical manifestations may also include hyperandrogenism, pleural effusion, ascites, or surgical emergency rarely as in our case.

Secondary amenorrhea, virilization, abdominal pain, or abdominal mass may be the presenting symptoms in post-pubertal girls.<sup>[5,6]</sup> Peritoneal rupture and recurrence are higher in post-pubertal girls.

Tumor staging is done with International Federation of Gynecology and Obstetrics (FIGO) system. Most tumors are unilateral and are FIGO stage 1 with sporadic origin. Syndromic associations are known.<sup>[7,8]</sup> Activating mutations of G alphas are present in 30%.<sup>[9]</sup> Tumors expressing FOXL2 present with precocious pseudopuberty. Disruption of SMAD1/5 or activation of SMAD2/3 has been linked to the pathogenesis.<sup>[10]</sup> Genetic aberrations seen include trisomy 12, 14, and monosomy 22.<sup>[11]</sup>

Tumors are capsulated with solid or cystic components. Extra capsular invasion is rare. JGCTOs are characterized by the presence of solid and follicular structures. Follicles have irregular size and shape. Neoplastic cells have ample eosinophilic cytoplasm, polymorphic nuclei, and mitotic figures. A positive immunohistochemical stain for inhibin is also diagnostic. Pathologic and immunohistochemical parameters may not decide the prognosis. Inhibin B and anti-Mullerian hormone are useful serum markers.<sup>[12]</sup>

Surgery is the mainstay of treatment. Adjuvant chemotherapy with cisplatin-based regimen is needed if the tumor is FIGO stage Ic and IIIc or has a high mitotic rate.

JGCTs have excellent cure rates. Five-year survival rates are 90-95% for FIGO stage I tumors and 25-50% for advanced stages. Age less than 10 years, presence of precocious pseudopuberty, FIGO stage I tumors, and FOXL2 expression are associated with good prognosis. Recurrences occur during the first 3 years after diagnosis. Stage I JGCTs are less likely to recur after surgery though late recurrences can occur even in stage I patients, necessitating long-term follow-up.

## CONCLUSION

We have reported a rare case of feminizing juvenile granulosa cell tumor of the ovary causing isosexual precocious puberty in a 7-year-old girl. Complete excision of the tumor led to normalization of hormonal levels and regression of secondary sexual characteristics.

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**Cite this article as:** Haroon NN, Agarwal G, Pandey R, Dabadghao P. Juvenile granulosa cell tumor presenting as isosexual precocious puberty: A case report and review of literature. *Indian J Endocr Metab* 2013;17:157-9.

**Source of Support:** Nil, **Conflict of Interest:** None declared.