

## Case report

### Juvenile Granulosa Cell Tumor Mimicking HAIR-AN in a 4-Year-Old: A Case Report

**Short Title:** JGCT Mimicking HAIR-AN in a 4-Year-Old

Rachel Choe Kim<sup>1</sup>, Iliya Goldberg<sup>2</sup>, Trevor Van Brunt<sup>3</sup>, Hamama Tul-Bushra<sup>4</sup>, Rebecca Batiste<sup>5</sup>, Andrew H. Lane<sup>6</sup>, Helen Hsieh<sup>7</sup>

<sup>1</sup>Renaissance School of Medicine, Stony Brook University, NY, United States

<sup>2</sup>Department of Surgery, Stony Brook Medicine, NY, United States

<sup>3</sup>Renaissance School of Medicine, Stony Brook University, NY, United States

<sup>4</sup>Department of Pathology, Stony Brook Medicine, NY, United States

<sup>5</sup>Department of Pathology, Stony Brook Medicine, NY, United States

<sup>6</sup>Department of Pediatrics, Stony Brook Children's Hospital, NY, United States

<sup>7</sup>Division of Pediatric Surgery, Department of Surgery, NY, United States

#### What is already known about this topic?

Juvenile Granulosa Cell Tumors typically present with pain, bloating, and a palpable mass on physical exam. They may also present with symptoms of precocious puberty and elevated serum estrogen or, less commonly, testosterone. Hyperandrogenism and hyperinsulinism are interrelated and may be seen in ovarian pathology, however the exact mechanism of this relationship is not fully known.

#### What is new?

Our case highlights an unusual androgen secreting JGCT accompanied by hyperinsulinemia in a prepubertal patient. Tumor removal resulted in resolution of hyperinsulinemia which may suggest that elevated testosterone may affect insulin levels.

#### ABSTRACT

Predominantly androgen secreting juvenile granulosa cell tumors (JGCT) are uncommon and few reports exist in the literature. We present a case of a JGCT which presented with signs of prepubertal hyperandrogenism and insulin resistance to highlight the possible interaction between hyperandrogenemia and hyperinsulinism. We conducted chart review of a rare androgen secreting JGCT accompanied by hyperinsulinemia in a prepubertal patient. A 4-year-old girl presented with acanthosis nigricans and hyperinsulinism mimicking the Hyperandrogenism Insulin Resistance and Acanthosis Nigricans (HAIR-AN) syndrome at an age much younger than is typical for this diagnosis. Laboratory studies revealed elevated insulin, inhibin A and B, and total testosterone. All laboratory results normalized after unilateral salpingo-oophorectomy. The final diagnosis was Stage IA JGCT. This case highlights the importance of including ovarian tumors in the differential diagnosis when considering causes of virilization and insulin resistance. Our case illustrates the potential relationship between excess testosterone secretion and hyperinsulinemia and strengthens evidence that hyperandrogenemia may promote hyperinsulinism in ovarian disease.

**Keywords:** Juvenile granulosa cell tumor, hyperandrogenism, insulin resistance

Helen Hsieh MD, Division of Pediatric Surgery, Department of Surgery, NY, United States  
ORCID 0000-0001-5226-1921

[Helen.hsieh@stonybrookmedicine.edu](mailto:Helen.hsieh@stonybrookmedicine.edu)

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## Introduction

Ten to twenty percent of all pediatric ovarian tumors are ovarian sex cord stromal tumors. A subtype of sex cord stromal tumors includes granulosa cell tumors which account for 70% of ovarian tumors in patients under the age of 20 years (1). A distinguishing feature of granulosa cell tumors is the secretion of estrogen (up to 97-98%), progesterone, and testosterone (2-3%) (2). Patients often present with symptoms of pain and bloating, with a palpable mass on physical exam and, those with JGCT may present with symptoms of precocious puberty and elevated serum estrogen (1). Increased expression of inhibin B may help distinguish JGCT from other causes of precocious puberty (3).

Type A insulin resistance syndrome is characterized by extreme insulin resistance, acanthosis nigricans, hirsutism and polycystic ovarian syndrome features in a non-obese patient (4). This syndrome has been described in females of all ages, with virilization present in infants and toddlers. Most cases are caused by insulin receptor mutations that reduce insulin affinity or insulin receptor tyrosine kinase activity (4). Treatment for insulin resistance syndrome is high doses of insulin. The clinically similar HAIR-AN syndrome typically presents in adolescence or adulthood and includes obesity, hyperandrogenism and is characterized by lack of insulin receptor mutations (5).

Here we present an illustrative case of a 4-year-old presenting with features associated with hyperinsulinemia and hyperandrogenism, which was caused by a rare virilizing juvenile granulosa cell tumor.

## Case Presentation

The patient presented at 4-years and 1-month of age with a 6-month history of abnormal hair growth on her arms, legs, and pubic area; greasy scalp hair; facial acne; and intermittent mood swings. Her parents noted increased irritability that accompanied changes to her appearance. The patient's birth history, past medical and developmental history were unremarkable. Of note, no genital ambiguity was noted at birth. The patient's mother had a history of hemochromatosis and polycystic ovarian syndrome (PCOS), and her maternal great-aunt and paternal great-grandmother had a history of ovarian cancer at advanced age. There was no family history of Type 2 diabetes mellitus or of precocious puberty, and the parents were not consanguineous. Physical exam revealed a height of 110.4 cm (97.3%/+1.9 SD), weight 29 kg (99.9%/+3.2 SD), and BMI 23.79 kg/m<sup>2</sup> (99.9%/+3.1 SD). The patient had extensive acanthosis nigricans on the back of her neck and in skinfold creases. She also had acne on her nose and chin, Tanner Stage 3 pubic hair, and thickened hair on her upper and lower extremities bilaterally. Lipomastia in the chest was consistent with her BMI, and there were no distinct breast buds. The patient had no clitoromegaly and the rest of her physical exam was within normal limits.

Initial laboratory evaluations were notable for an elevated free testosterone, lactic dehydrogenase (LDH), anti-Mullerian hormone, 17-OH-progesterone, insulin, inhibin B, and inhibin A (Table 1).  $\beta$ -hCG,  $\alpha$ -fetoprotein (AFP), and CA-125 were all within normal limits. FSH was low, and the remainder of her labs were unremarkable (Table 1). Her bone age was 6-years and 4-months (chronological age 4-years and 1-month) as determined by interdisciplinary collaboration through evaluation by radiology and pediatric endocrinology using the method of Greulich and Pyle.

Pelvic ultrasound demonstrated a heterogeneous hypoechoic solid vascular mass measuring 6.3 cm x 3.4 cm x 7.1 cm in the left adnexa with a normal right ovary with no cysts noted. A computed tomography (CT) of the pelvis demonstrated a heterogeneous, solid, left sided ovarian mass measuring 4.4 cm x 4.6 cm x 4.2 cm without intense enhancement and no evidence of metastatic disease or lymphadenopathy. The uterus was noted to be large for her age with the fundus larger than the cervix (Figure 1).

After unilateral salpingo-oophorectomy was performed, inhibin A, inhibin B, 17-OH progesterone, testosterone, anti-Mullerian hormone, and insulin hormone levels normalized (Table 1). Most recently in follow-up at the age of 6 years 3 months, her height was 129.5 cm (99.1%/+2.4 SD), weight 48.8 kg (99.9%/+3.4 SD), and BMI 29.1 kg/m<sup>2</sup> (99.8%/+2.9 SD). The acanthosis nigricans had substantially regressed. Her acne and hirsutism had completely resolved. Ultrasound showed a normal uterus and right ovary with no residual adnexal mass. Her bone age was 7-years and 10-months at the chronological age of 6-years.

## Discussion

Our patient's extensive acanthosis and virilization was observed at an age typical for onset of Type A insulin resistance, but too young to qualify as HAIR-AN (5). However, her obesity and modestly elevated insulin levels (significantly lower than values generally reported in Type A insulin resistance) made a diagnosis of Type A less likely. Because neither of these diagnoses fit the patient's presentation (obesity, moderate insulin levels, advanced bone age), laboratory and radiological studies were obtained which revealed a testosterone secreting JGCT with accompanying hyperinsulinemia. There is evidence that some JGCTs are associated with a heritable DICER1 mutation, however, our patient did not fit the clinical picture for DICER1 syndrome (6, 7). The distant family history of ovarian cancer was associated with advanced age and is unlikely to represent genetic predisposition in our patient.

Granulosa cell tumors are rare, accounting for about 5% of pediatric ovarian tumors with an incidence of 2.6 per 100,000 females every year (1). Hormonally active JGCTs most often secrete estrogen which leads to premature breast development, but they can also secrete androgens, which results in virilization. Kalfa et al. identified 6 patients with JGCT associated with hyperandrogenism and found that all tumors had either absent or significantly decreased intra-tumoral expression of aromatase, suggesting that increased testosterone production may be attributed to decreased conversion of androgens into estrogens within these tumors (3).

We speculate that in this patient, testosterone secretion led to the hyperinsulinism and substantial acanthosis nigricans, because her fasting insulin declined and her acanthosis nigricans improved after complete resection of the tumor. Her increased weight may have also contributed to her initial hyperinsulinemia, however on follow up her insulin levels had normalized despite her BMI increasing. Additionally, clinical findings of hyperinsulinemia are not typically seen in overweight children of this age. We found only three reports of JGCT that presented with increased insulin, all of which were accompanied by hyperandrogenism. Larizzi et al. describe a 16-year-old female presenting with secondary amenorrhea, high

dehydroepiandrosterone (DHEA), 17-hydroxyprogesterone (17OH-P), and insulin, who was found to have a JGCT (8). Ovulation resumed ten days after the tumor was removed, and DHEA, 17OH-P, and insulin returned to normal levels at post-operative follow up. Kwiatkowska et al. report a case of JGCT in a 17-year-old female who presented with elevated testosterone and insulin. Testosterone levels subsequently decreased after tumor excision. Insulin levels post-operatively were not reported (9). Brisigotti et al. identified a 7-week-old patient with Donohue syndrome who had clinical hyperandrogenism, hyperinsulinemia, and bilateral JGCTs (10). Unfortunately, the patient died two days after resection of the JGCTs, so no data is available as to whether hyperandrogenism and hyperinsulinemia resolved following the surgery; our patient did not meet clinical criteria for Donohue syndrome.

The extent to which hyperandrogenemia and hyperinsulinemia reciprocally influence each other is an area of active research. Although testosterone has been shown to cause insulin hypersecretion through androgen receptor signaling (11), others hypothesize that increased insulin production induces ovarian hyperandrogenism in diseases such as PCOS (12). Mishra et al. demonstrated that increased exposure to androgens results in hyperinsulinemia in female rats through dose dependent upregulation of the insulin gene (*Ins*) (11). They identified an androgen receptor binding site on the promoter region of *Ins*, which they hypothesize facilitates this response. Huang-Doran et al. found that GnRH agonists reduced androgen levels in patients with severe insulin resistance without affecting insulin sensitivity, suggesting that hyperinsulinism is the main driver of hyperandrogenism in individuals with insulin resistance (12). In contrast to our patient's age (4-years), their study focused on patients over the age of 10-years with a presumed mature hypothalamic-pituitary-gonadal axis (HPGA) (12). Our case provides insight into the relationship between hyperandrogenism and hyperinsulinemia because the patient presented at a young age with an immature HPGA, allowing a unique perspective on the relationship between androgens and hyperinsulinism in the absence of gonadotropins. This case report suggests that excess androgen production in a prepubertal female may result in increased insulin production.

### **Conclusion**

We report a case of an androgen secreting JGCT which mimicked HAIR-AN/Type 1A insulin resistance. This case emphasizes the importance of a broad differential when considering potential causes of virilization and insulin resistance and highlights the possible relationship between testosterone secretion and hyperinsulinemia.

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**Table 1: Preoperative and Postoperative Laboratory Values**

	Pre-operative	Within 2 Weeks Post-operative	6 Months - 1 Year Post-operative	Normal Reference	Units
LDH	363	261	-	94 - 250	IU/L
AMH	6.75	4.306	2.98	0.256 - 6.345	ng/mL
Inhibin A	43.7	1.4	-	<7-14	pg/mL
Inhibin B	1715	25	15.2	<73.0	pg/mL
AFP	4	-	-	<8.0	Ng/mL
CA125	13.6	-	-	0.0 - 38.0	ug/dL
β-HCG	<1	-	-	0 - 5	mIU/mL
FSH	<0.017	<0.1	-	1.0 - 4.2	mIU/mL
LH	<0.005	-	-	0.02-0.3	mIU/mL
Estradiol	11.8	-	<5	0-14.9	pg/mL
17-OH-progesterone	145	<10.00	-	0 - 90	ng/dL
DHEA-S	21.4	-	-	1.8 - 97.2	ug/dL

Testosterone, Total	205.6	<1	4	≤20	ng/dL
Insulin	45.2	2	17	2.6 - 24.9	uIU/mL

Uncorrected proof