CASE REPORT

DOI: 10.4274/jcrpe.galenos.2022.2022-4-17

J Clin Res Pediatr Endocrinol 2024;16(2):200-204

Juvenile Granulosa Cell Tumor Mimicking HAIR-AN in a 4-year-old: A Case Report

Rachel Choe Kim[1], Ilya Goldberg[2], Trevor Van Brunt[1], Hamama Tul-Bushra[3], Rebecca Batiste[3], Andrew H. Lane[4], Helen Hsieh[5]

[1]Stony Brook University, Renaissance Faculty of Medicine, New York, USA
[2]Stony Brook University, Renaissance Faculty of Medicine, Department of Surgery, New York, USA
[3]Stony Brook University, Renaissance Faculty of Medicine, Department of Pathology, New York, USA
[4]Stony Brook Children's Hospital, Clinic of Pediatrics, New York, USA
[5]Stony Brook University, Renaissance Faculty of Medicine, Department of Surgery, Division of Pediatric Surgery, New York, USA

What is already known on 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 but the exact mechanism of this relationship is not fully understood.

What this study adds?

This is a case of an unusual androgen secreting juvenile granulosa cell tumors accompanied by hyperinsulinemia in a prepubertal patient. Tumor removal resulted in resolution of hyperinsulinemia, which suggests that elevated testosterone may affect insulin levels.

Abstract

Predominantly androgen secreting juvenile granulosa cell tumors (JGCT) are uncommon and few reports have been published. We present a case of a JGCT that presented with signs of prepubertal hyperandrogenism and insulin resistance to highlight the possible interaction between hyperandrogenemia and hyperinsulinism. A 4-year-old girl presented with acanthosis nigricans and hyperinsulinism, mimicking the hyperandrogenism, insulin resistance and acanthosis nigricans 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 1A JGCT. This case highlights the importance of including ovarian tumors in the differential diagnosis when considering causes of virilization and insulin resistance. This case also suggests a 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

Address for Correspondence: Helen Hsieh MD, Stony Brook University, Renaissance Faculty of Medicine, Department of Surgery, Division of Pediatric Surgery, New York, USA
Phone: +631-601-7874 **E-mail:** Helen.hsieh@stonybrookmedicine.edu **ORCID:** orcid.org/0000-0001-5226-1921

Conflict of interest: None declared.
Received: 15.04.2022
Accepted: 31.07.2022

Introduction

Ten to twenty percent of all pediatric ovarian tumors are ovarian sex cord stromal tumors. A subtype of sex cord stromal tumors, which account for 70% of ovarian tumors in patients under the age of 20 years, includes granulosa cell tumors (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 juvenile granulosa cell tumor (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 other features of polycystic ovarian syndrome (PCOS) 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 hyperandrogenism, insulin resistance and acanthosis nigricans (HAIR-AN) syndrome typically presents in adolescence or adulthood and includes obesity, hyperandrogenism and is characterized by the 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 JGCT.

Case Report

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 PCOS, and her maternal great-aunt and paternal great-grandmother had a history of ovarian cancer at advanced ages. 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 standard deviation (SD)], weight 29 kg (99.9% / +3.2 SD), and body mass index (BMI) 23.79 kg/m^2 (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

Table 1. Pre-operative and post-operative laboratory values

	Pre-operative	Within 2 weeks post-operative	Six 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

LDH: lactate dehydrogenase, AMH: anti-Mullerian hormone, AFP: alpha-fetoprotein, FSH: follicle stimulating hormone, LH: luteinizing hormone, DHEA-S: dehydroepiandrosterone sulfate

had no clitoromegaly and the rest of her physical exam was within normal limits.

Initial laboratory evaluations were notable for an elevated free testosterone, lactate dehydrogenase, anti-Mullerian hormone, 17-hydroxyprogesterone (17-OH-P), insulin, inhibin B, and inhibin A (Table 1). β-hCG, α-fetoprotein, and CA-125 were all within normal limits. Follicle stimulating hormone level was low, and the remainder of her laboratory results 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 investigation 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-P, testosterone, anti-Mullerian hormone, and insulin 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^2 (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 nigricans 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. As neither of these diagnoses fitted 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 DICER syndrome (6,7). The distant family history of ovarian cancer was

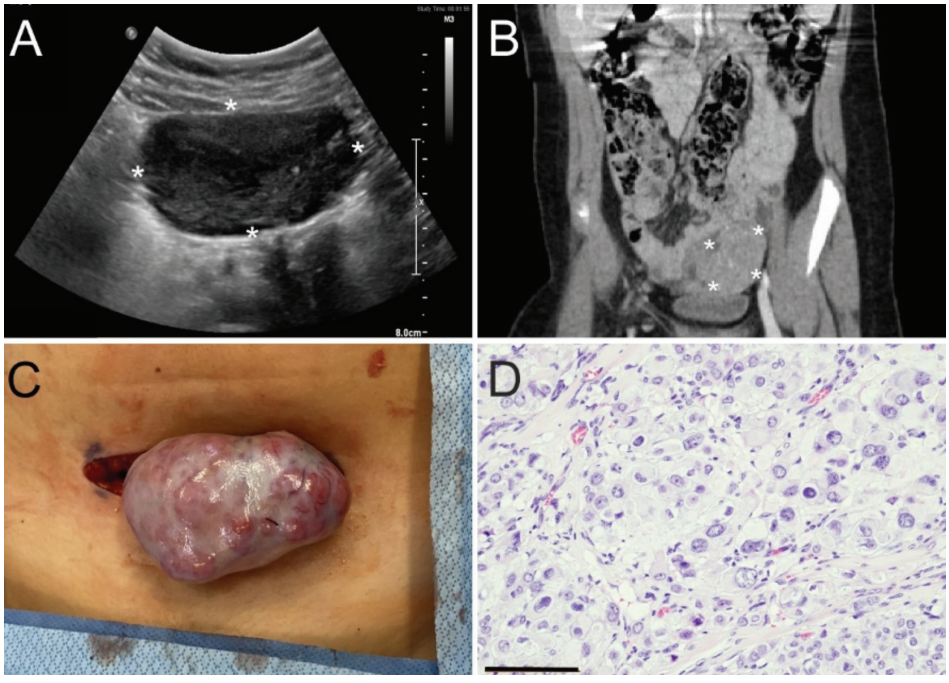

Figure 1. A) Sagittal ultrasound view of left ovarian lesion (outlined with *), **B)** Coronal view of CT abdomen-pelvis demonstrating solid left adnexal lesion (outlined with *), **C)** Left adnexal mass delivered through Pfannenstiel incision, **D)** Hematoxylin and eosin staining of JGCT demonstrating pleomorphic cells. Immunohistochemistry (data not shown) was positive for inhibin, and negative for pancytokeratin, WT1 and calretinin

CT: computed tomography, JGCT: juvenile granulosa cell tumors

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. (3) identified six 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.

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. Larizza et al. (8) described a 16-year-old female presenting with secondary amenorrhea, high dehydroepiandrosterone (DHEA), 17-OH-P, and insulin who was found to have a JGCT. Ovulation resumed ten days after the tumor was removed, and DHEA, 17-OH-P, and insulin returned to normal levels at post-operative follow up. Kwiatkowska et al. (9) 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. Post-operative insulin levels were not reported. Brisigotti et al. (10) identified a 7-week-old patient with Donohue syndrome who had clinical hyperandrogenism, hyperinsulinemia, and bilateral JGCTs. 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. The present case 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 have hypothesized that increased insulin production induces ovarian hyperandrogenism in conditions such as PCOS (12). Mishra et al. (11) demonstrated that increased exposure to androgens resulted in hyperinsulinemia in female rats through dose-dependent upregulation of the insulin gene (*Ins*). They identified an androgen receptor binding site on the promoter region of *Ins,* which they hypothesize facilitates this response. Huang-Doran et al. (12) found that gonadotropin releasing hormone 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. 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). The presented 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.

Acknowledgements

We appreciate that the family has generously provided informed consent for this case report.

Ethics

Informed Consent: Informed written consent form was obtained from parents before participating the study.

Authorship Contributions

Data Collection or Processing: Rachel Choe Kim, Hamama Tul-Bushra, Rebecca Batiste, Andrew H. Lane, Helen Hsieh, Analysis or Interpretation: Rachel Choe Kim, Andrew H. Lane, Helen Hsieh, Literature Search: Rachel Choe Kim, Ilya Goldberg, Andrew H. Lane, Helen Hsieh, Writing: Rachel Choe Kim, Ilya Goldberg, Trevor Van Brunt, Andrew H. Lane, Helen Hsieh.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Heo SH, Kim JW, Shin SS, Jeong SI, Lim HS, Choi YD, Lee KH, Kang WD, Jeong YY, Kang HK. Review of ovarian tumors in children and adolescents: radiologic-pathologic correlation. Radiographics 2014;34:2039-2055.
2. Bús D, Buzogány M, Nagy G, Vajda G. Rare virilizing granulosa cell tumor in an adolescent. Mol Clin Oncol 2017;6:88-90. Epub 2016 Nov 18
3. Kalfa N, Méduri G, Philibert P, Patte C, Boizet-Bonhoure B, Thibaut E, Pienkowski C, Jaubert F, Misrahi M, Sultan C. Unusual virilization in girls with juvenile granulosa cell tumors of the ovary is related to intratumoral aromatase deficiency. Horm Res Paediatr 2010;74:83-91. Epub 2010 Apr 15
4. Musso C, Cochran E, Moran SA, Skarulis MC, Oral EA, Taylor S, Gorden P. Clinical course of genetic diseases of the insulin receptor (type A and Rabson-Mendenhall syndromes): a 30-year prospective. Medicine (Baltimore) 2004;83:209-222.
5. Elmer KB, George RM. HAIR-AN syndrome: a multisystem challenge. Am Fam Physician 2001;63:2385-2390.
6. Schultz KAP, Harris AK, Finch M, Dehner LP, Brown JB, Gershenson DM, Young RH, Field A, Yu W, Turner J, Cost NG, Schneider DT, Stewart DR, Frazier AL, Messinger Y, Hill DA. DICER1-related Sertoli-Leydig cell tumor and gynandroblastoma: Clinical and genetic findings from the International Ovarian and Testicular Stromal Tumor Registry. Gynecol Oncol 2017;147:521-527. Epub 2017 Oct 14
7. Baillard P, Genestie C, Croce S, Descotes F, Rouleau E, Treilleux I, Gouy S, Morice P, Ray-Coquard I, McCluggage WG, Devouassoux-Shisheboran M. Rare DICER1 and Absent FOXL2 Mutations Characterize Ovarian Juvenile Granulosa Cell Tumors. Am J Surg Pathol 2021;45:223-229.
8. Larizza D, Calcaterra V, Sampaolo P, Lanati G, Brambilla P, Mondello T, Cesari S. Unusual presentation of juvenile granulosa cell tumor of the ovary. J Endocrinol Invest 2006;29:653-656.
9. Kwiatkowska A, Kułak K, Wertel I. Gender Dysphoria Disrupting the Course of Treatment of a Recurrent Juvenile Granulosa Cell Tumor in an Adolescent Female: A Case Report. Case Rep Oncol 2020;13:1330-1336.
10. Brisigotti M, Fabbretti G, Pesce F, Gatti R, Cohen A, Parenti G, Callea F. Congenital bilateral juvenile granulosa cell tumor of the ovary in leprechaunism: a case report. Pediatr Pathol 1993;13:549-558.
11. Mishra JS, More AS, Kumar S. Elevated androgen levels induce hyperinsulinemia through increase in Ins1 transcription in pancreatic beta cells in female rats. Biol Reprod 2018;98:520-531.
12. Huang-Doran I, Kinzer AB, Jimenez-Linan M, Thackray K, Harris J, Adams CL, de Kerdanet M, Stears A, O'Rahilly S, Savage DB, Gorden P, Brown RJ, Semple RK. Ovarian Hyperandrogenism and Response to Gonadotropin-releasing Hormone Analogues in Primary Severe Insulin Resistance. J Clin Endocrinol Metab 2021;106:2367-2383.