AACE Clinical Case Rep. 7 (2021) 261–263

Contents lists available at ScienceDirect

AACE Clinical Case Reports

journal homepage: www.aaceclinicalcasereports.com

Case Report

Ovarian Steroid Cell Tumor Masquerading as Steroid-Unresponsive Congenital Adrenal Hyperplasia

Jane E. Driano, BA [1], Ana L. Creo, MD [2], Seema Kumar, MD [2], Asma J. Chattha, MBBS [3], Aida N. Lteif, MD [2,*]

[1] Creighton University School of Medicine, Omaha, Nebraska
[2] Division of Pediatric Endocrinology and Metabolism
[3] Division of Pediatric Gynecology, Mayo Clinic, Rochester, Minnesota

ARTICLE INFO

Article history:
Received 27 October 2020
Received in revised form
5 February 2021
Accepted 8 February 2021
Available online 17 February 2021

Key words:
17 hydroxyprogesterone S
steroid cell tumor
venous sampling

ABSTRACT

Objective: Ovarian neoplasms in children are rare. The objective of this report is to emphasize the importance of considering those neoplasms in the differential diagnosis of hyperandrogenism even with negative diagnostic imaging.
Methods: We report the case of a 12-year-old girl who presented with virilization and elevated 17 hydroxyprogesterone (17-OHP) and who was subsequently diagnosed with an ovarian neoplasm.
Results: The patient was initially seen for hirsutism and deepening of the voice. Elevated 17-OHP, androstenedione, and testosterone prompted the initial diagnosis of nonclassic congenital adrenal hyperplasia due to 21-hydroxylase deficiency, but those levels failed to suppress on corticosteroid therapy. Ultrasound, computed tomography scan, and magnetic resonance imaging of the abdomen and pelvis were normal. Genetic testing for congenital adrenal hyperplasia was negative. Bilateral selective adrenal and ovarian venous sampling confirmed the ovarian origin of her hyperandrogenism. A unilateral salpingo-oophorectomy revealed a steroid cell tumor. Postoperatively there was normalization of testosterone and 17-OHP.
Conclusion: This report highlights the utility of selective adrenal and ovarian sampling when suspecting a primary androgen-secreting neoplasm, even in the setting of elevated 17-OHP levels and negative imaging studies, as early diagnosis can prevent manifestation of irreversible symptoms of virilization

Introduction

Female hyperandrogenism may arise from gonadal and adrenal pathologies, including congenital adrenal hyperplasia (CAH) and androgen-secreting neoplasms (ASN). While elevation in 17-hydroxyprogesterone (17-OHP) levels is suggestive of CAH 21-hydroxylase deficiency, there have been reports of steroid cell tumors (SCTs) presenting with hyperandrogenism and elevated 17-OHP.[1–7] Refractory cases of CAH to steroid therapy warrant further investigation into the cause of virilization, even in the presence of negative imaging. In this report, we describe the utility of selective venous sampling in the diagnosis of a female adolescent who presented with virilization secondary to an SCT masquerading as CAH.

Case Report

A 12-year-old girl presented with complaints of hirsutism, voice deepening, increased muscle strength, and lack of breast development. Pubic hair was first noted around age 6 years. On examination, the patient was normotensive. She had marked hirsutism and mild facial acne. Breasts and pubic hair were in Tanner stages 2 and 4, respectively. Clitoromegaly was noted. Initial hormonal testing revealed a marked elevation of 17-OHP, androstenedione, and total testosterone, quantified by chromatography-tandem mass spectrometry (Table 1). Adrenocorticotrophic hormone (ACTH), 11 deoxycortisol, and dehydroepiandrostenedione sulfate (DHEA-S) were normal. Bone age was 15 years. Pelvic ultrasound showed normal appearing ovaries and uterus. Hydrocortisone was initiated

* Address correspondence and reprint requests to Aida N. Lteif, Division of Pediatric Endocrinology and Metabolism, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.
E-mail address: lteif.aida@mayo.edu (A.N. Lteif).

https://doi.org/10.1016/j.aace.2021.02.001

Table 1
Laboratory Values at Presentation and Follow-Up

	17-OHP (ng/dL)	T (ng/dL)	AS (ng/dL)	DHEA-S (mcg/dL)	ACTH (pg/mL)	Cortisol (mcg/dL)
Reference values	<80-285	<7-75	80-190	17-343	7.2-63	7-25
Baseline	976	172	670	124	12	8
On hydrocortisone 25 mg/m^2/day	1670	147	879	107		
Off Therapy	974	169	418			16
2 weeks postop	98	14	71			
1 year postop	89	<7	68			
3 years postop	<40	11	34			

Abbreviations: 17-OHP = 17 hydroxy progesterone; ACTH = adrenocorticotropic hormone; AS = androstenedione; DHEA-S = dehydroepiandrostenedione sulfate; T = testosterone.

at 16 mg/m^2/day and dosing was incrementally increased to 26 mg/m2/day for a diagnosis of nonclassic CAH. The patient's symptoms failed to improve on therapy and 17-OHP paradoxically increased (Table 1). Computed tomography (CT) followed by magnetic resonance imaging (MRI) of the abdomen and pelvis were then obtained and were normal. The ovaries measured 3.2 x 1.0 x 1.0 cm on the right and 3 x 1.4 x 1.1 cm on the left with numerous peripheral follicles. Because of the nondiagnostic imaging studies, a CYP21A2 gene analysis was done and revealed no disease-causing mutations. Hydrocortisone was gradually decreased and then discontinued. To identify the source of elevated androgens, bilateral selective adrenal and ovarian effluent venous sampling was performed 3 months later. The results localized the source of hyperandrogenism and 17-OHP to the right ovarian vein (Table 2). Carcinoembryonic antigen and alpha fetoprotein levels were normal. The patient underwent laparoscopic surgery for a right salpingo-oophorectomy. Final pathological diagnosis confirmed the presence of a 4.8 x 2.3 x 2.1 cm ovarian SCT. After resection, 17-OHP, androstenedione, and testosterone levels normalized.

Discussion

This case provides insight into the similarities in clinical presentation between CAH and androgen-secreting ovarian SCTs. The latter have been classified as primary virilizing tumors, similar to our patient, ovarian adrenal rest tumors, or coexisting with CAH.[8,9] It also demonstrates the efficacy of selective venous sampling for localization of hyperandrogenism in a pediatric patient with negative imaging studies.

SCTs are rare, especially in pediatrics.[4] About two thirds of SCTs are not otherwise specified (NOS). SCTs NOS are of stromal cell origin with variable histological features.[6] The ovarian tumor from this case had abundant cytoplasm with fibrous bands of inflammation. Conversely, SCTs can also be classified as Leydig cell tumors with cytoplasmic crystals of Reinke, which the presented tumor lacked. These tumors are usually benign and have been described to cause virilization, with hyperandrogenism noted in 56% to 77% of affected patients.[4] Our patient presented with hyperandrogenism and consequential gonadotropin suppression, as demonstrated by the lack of significant breast tissue development.

Wong et al[6] recently reviewed 21 case reports of SCTs, NOS, with 17-OHP concentrations reported and found a prevalence of 81% of elevated 17-OHP, similar to our patient. Yılmaz-Agladıoglu et al[7] reported a 13-year-old female who experienced a 6 year delay in diagnosis of SCT, NOS, by ultrasound due to presumed CAH. Yoshimatsu et al[10] documented an ovarian tumor, diagnosed as SCT, NOS, visualized on CT and MRI in a 4-year-old girl with virilization. These cases differed from ours as diagnostic imaging studies were positive. Some also presented with hypercortisolism, gynecomastia, irregular vaginal bleeding, and hypertension.

SCTs may form as ovarian adrenal rest tumors secondary to undiagnosed CAH, poor medication compliance, Nelson syndrome, or other associations with ACTH hypersecretion.[8,11] Residual adrenal tissue can reside along the migratory pathway of the adrenal gland away from its embryonic location near the gonads. Elevated ACTH concentrations or other steroidogenic enzyme defects may inappropriately stimulate the adrenal tissue, creating functional ectopic adrenal glands.[8,9] Thomas et al[8] reported persistent testosterone and 17-OHP elevation in a 17-year-old girl with CAH and poor medication compliance. An ultrasound revealed an ovarian tumor, which upon resection was diagnosed as an SCT, NOS. Due to elevated ACTH, it was classified as an ovarian adrenal rest tumor. The normal ACTH upon presentation precluded an ovarian adrenal rest tumor in our patient.

Solish et al[5] presented a similar case to ours in which a 3.5-year-old boy with early virilization, elevated 17-OHP, and a testicular mass was diagnosed with a Leydig cell tumor although CAH and a testicular adrenal rest tumor were originally suspected. Molecular analysis of the tumor revealed large amounts of P450scc mRNA, which codes for the cholesterol side-chain cleavage enzyme, leading to excess pregnenolone and subsequently 17-OHP. Primary ASNs are difficult to distinguish histologically from adrenal rest tumors as they have the same embryonic origin, the gonadal ridge. Thus, other clinical signs and symptoms, particularly postoperatively, can help in differentiating them.[5]

Early diagnosis and treatment of ASN can prevent irreversible symptoms of hyperandrogenism, such as short stature.[7] Differentiating between ASN and CAH can be challenging, with many of the diagnostic pitfalls highlighted in our case. Rapid virilization with severe signs such as a deepening voice, male pattern baldness, and clitoromegaly are associated with ASN over CAH in females.[6,12]

Diagnostic tools beyond serum androgen levels include the ACTH stimulation test, molecular testing, urinary steroid profile, and imaging.[6] A stimulated 17-OHP of >1000 ng/dL is usually diagnostic for CAH. However, paradoxical responses by virilizing ovarian tumors to ACTH stimulation have been reported due to the presence of ACTH receptors on an ASN.[6] The normal DHEA-S level in our patient was suggestive but not diagnostic of an ovarian pathology. Children with classic and nonclassic CAH have been reported to have markedly elevated testosterone with normal DHEA-S.[13] Even though our patient's testosterone was in a range suggestive of a tumor or classic CAH, nonclassic CAH was still in the differential as patients who are compound heterozygotes can have significant virilization.[14]

Because of the ambiguity of diagnostic testing and negative imaging, the decision to pursue genetic testing was made prior to proceeding with selective venous sampling, which was felt to be more invasive.

Ultrasound, MRI, and CT are performed for investigation of ovarian tumor. Fanta et al[15] argue for reduced reliance on these techniques. Sarfati et al[16] proposed positive and negative predictive values of an ultrasound in diagnosing an ovarian ASN as 71% and 73%, respectively, and 78% and 100%, respectively, with

Table 2
17-OHP (ng/dL) and Testosterone (ng/dL) During Venous Sampling

	Baseline	Right ovarian vein	Left ovarian vein	Right adrenal vein	Left adrenal vein
17 OHP ng/dL	1170	120 000	1570	663	592
Testosterone ng/dL	192	3650	134	111	103

Abbreviation: 17-OHP = 17 hydroxy progesterone.

MRI. However, imaging could yield false negatives due to ASN's solid texture and size, as our case demonstrated.[17] If an ovarian tumor is seen on imaging, CAH cannot be excluded due to a potential adrenal rest tumor.[9] Additionally, ASN can coexist with CAH. If virilization persists after resection, medical history and clinical signs and symptoms may be helpful in differentiating an ovarian adrenal rest tumor from a primary ASN in the presence of CAH.[8,9] For cases in which imaging is inconclusive, selective venous sampling may localize the source of androgen, similar to the presented case.[17]

Few cases have been described in the literature in which selective venous sampling was utilized as a diagnostic tool in pediatrics. Levens et al[18] conducted selective venous sampling on a pediatric patient and confirmed hyperandrogenism from the polycystic right ovary as was seen on imaging. White et al[19] reported a child with bilateral Sertoli-Leydig cell tumors diagnosed with imaging and selective venous sampling. These cases differ from ours due to positive imaging studies prior to venous sampling.

Selective venous sampling for localization of an ASN is done by catheterization of the right and left ovarian and adrenal veins. Levens et al[18] analyzed the diagnostic ability of selective venous catheterization in localizing the source of female hyperandrogenism. They found that in the presence of a serum testosterone $\geq$4.51 nmol/L, a ratio of right:left ovarian testosterone $\geq$1.44 correctly identified 90% of right-sided tumors and that 86% of women with left-sided or bilateral lesions had a lower value. The ratio of right:left ovarian testosterone in our patient was approximately 76, strongly indicating a right-sided ovarian ASN. If an adrenal ASN is the cause, a ratio of ipsilateral adrenal testosterone:peripheral testosterone >2 is expected.[20]

Androgen levels typically normalize following tumor resection. Further research is needed to diagnose virilization secondary to ASN and explore techniques for improving the localization of 17-OHP hypersecretion with less invasive ways than selective venous sampling.

Conclusion

The patient's age, presentation as CAH, negative imaging studies, and necessity of selective venous sampling make our patient's case exceedingly rare. A primary ASN may need to be considered as an underlying cause of hyperandrogenism even in the setting of elevated 17-OHP levels. Further investigation is warranted with a failed response to steroid therapy or a normal genetic analysis. Venous sampling should be considered for patients with unremarkable imaging. Early diagnosis and management of the cause of female androgen excess can prevent manifestation of irreversible symptoms of virilization.

Disclosure

No funding was secured for this study.

Acknowledgment

The authors have no financial relationships relevant to this article to disclose.

References

1. Amato G, Izzo G, Izzo A. A paradoxical inhibition of androgenic hyperproduction by a Sertoli-Leydig cell tumour ovary. *Hum Reprod*. 1995;10(11):2967–2969.
2. Bercovici JP, Tater D, Khoury S, Charles JF, Floch J, Leroy JP. Leydig cell tumor with gynecomastia: hormonal effects of an estrogen-producing tumor. *J Clin Endocrinol Metab*. 1981;53(6):1291–1296.
3. Mineur P, De Cooman S, Hustin J, Verhoeven G, De Hertogh R. Feminizing testicular Leydig cell tumor: hormonal profile before and after unilateral orchidectomy. *J Clin Endocrinol Metab*. 1987;64(4):686–691.
4. Qian L, Shen Z, Zhang X, Wu D, Zhou Y. Ovarian steroid cell tumor, not otherwise specified: a case report and literature review. *Mol Clin Oncol*. 2016;5(6):839–841.
5. Solish SB, Goldsmith MA, Voutilainen R, Miller WL. Molecular characterization of a Leydig cell tumor presenting as congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 1989;69(6):1148–1152.
6. Wong FCK, Chan AZ, Wong WS, et al. Hyperandrogenism, elevated 17-hydroxyprogesterone and its urinary metabolites in a young woman with ovarian steroid cell tumor, not otherwise specified: case report and review of the literature. *Case Rep Endocrinol*. 2019;2019:9237459.
7. Yılmaz-Ağladıoğlu S, Savaş-Erdeve Ş, Boduroğlu E, et al. A girl with steroid cell ovarian tumor misdiagnosed as non-classical congenital adrenal hyperplasia. *Turk J Pediatr*. 2013;55(4):443–446.
8. Thomas TT, Ruscher KR, Mandavilli S, Balarezo F, Finck CM. Ovarian steroid cell tumor, not otherwise specified, associated with congenital adrenal hyperplasia: rare tumors of an endocrine disease. *J Pediatr Surg*. 2013;48(6):E23–E27.
9. Fernández-García Salazar R, Muñoz-Darias C, Haro-Mora JJ, et al. Woman with virilizing congenital adrenal hyperplasia and Leydig cell tumor of the ovary. *Gynecol Endocrinol*. 2014;30(8):549–552.
10. Yoshimatsu T, Nagai K, Miyawaki R, et al. Malignant ovarian steroid cell tumor, not otherwise specified, causes virilization in a 4-year-old girl: a case report and literature review. *Case Rep Oncol*. 2020;13(1):358–364.
11. Tiosano D, Vlodavsky E, Filmar S, Weiner Z, Goldsher D, Bar-Shalom R. Ovarian adrenal rest tumor in a congenital adrenal hyperplasia patient with adrenocorticotropin hypersecretion following adrenalectomy. *Horm Res Paediatr*. 2010;74(3):223–228.
12. Gheorghisan-Galateanu A, Fica S, Terzea DC, Caragheorgheopol A, Horhoianu V. Sertoli-Leydig cell tumor - a rare androgen-secreting ovarian tumor in postmenopausal women. Case report and review of literature. *J Cell Mol Med*. 2003;7(4):461–471.
13. Golden MP, Lippe BM, Kaplan SA, Lavin N, Slavin J. Management of congenital adrenal hyperplasia using serum dehydroepiandrosterone sulfate and 17-hydroxyprogesterone concentrations. *Pediatrics*. 1978;61(6):867–871.
14. Livadas S, Dracopoulou M, Dastamani A, et al. The spectrum of clinical, hormonal and molecular findings in 280 individuals with nonclassical congenital adrenal hyperplasia caused by mutations of the CYP21A2 gene. *Clin Endocrinol*. 2015;82(4):543–549.
15. Fanta M, Fischerová D, Indrielle-Kelly T, et al. Diagnostic pitfalls in ovarian androgen-secreting (Leydig cell) tumours: case series. *J Obstet Gynaecol*. 2019;39(3):359–364.
16. Sarfati J, Bachelot A, Coussieu C, Meduri G, Touraine P, Women SGHiP. Impact of clinical, hormonal, radiological, and immunohistochemical studies on the diagnosis of postmenopausal hyperandrogenism. *Eur J Endocrinol*. 2011;165(5):779–788.
17. Inoue Y, Kamura T, Okuma A, et al. Efficacy of selective venous sampling to localize a small ovarian androgen-producing tumor. *J Obstet Gynaecol Res*. 1999;25(4):231–236.
18. Levens ED, Whitcomb BW, Csokmay JM, Nieman LK. Selective venous sampling for androgen-producing ovarian pathology. *Clin Endocrinol*. 2009;70(4):606–614.
19. White LC, Buchanan KD, O'Leary TD, Carlan SJ, Boothby R. Direct laparoscopic venous sampling to diagnose a small Sertoli-Leydig tumor. *Gynecol Oncol*. 2003;91(1):254–257.
20. Monroe EJ, Carney BW, Ingraham CR, Johnson GE, Valji K. An interventionist's guide to endocrine consultations. *Radiographics*. 2017;37(4):1246–1267.