Case Report

Selective Venous Sampling Prompting Unilateral Oophorectomy in an Adolescent With PCOS and Markedly Elevated Testosterone

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ABSTRACT

Background: For adolescents with suspected polycystic ovary syndrome (PCOS) and severely elevated testosterone concentrations, imaging is recommended to assess for neoplasm. Selective venous sampling (SVS) can be considered when imaging is nondiagnostic.
Case: An adolescent female treated for PCOS had a peak testosterone of 344 ng/dL (11.9 nmol/L). Imaging did not localize a mass. SVS implicated the right ovary as the source of hyperandrogenism. Following laparoscopic right oophorectomy, pathology excluded a neoplasm and confirmed PCOS. She subsequently had rapid and persistent improvement in her hyperandrogenism.
Summary and Conclusion: Striking testosterone elevation can occur with adolescent PCOS. SVS is a tool for localizing the source of severe hyperandrogenism, yet unilaterality is not always diagnostic of a neoplasm. Unilateral oophorectomy could nonetheless be therapeutic for severe PCOS.
Key Words: Hyperandrogenism, Adolescent, Polycystic ovary syndrome, Peripheral catheterization, Oophorectomy

Introduction

Polycystic ovary syndrome (PCOS) is a common cause of hyperandrogenism in youth. Expert guidelines suggest measurement of serum testosterone in the evaluation for PCOS and to consider an androgen-producing tumor if total testosterone levels are greater than 150-200 ng/dL.[1,2] The recommended evaluation includes diagnostic imaging, such as pelvic ultrasonography of the ovaries and/or computed tomography of the adrenal glands to localize a neoplasm. However, guidelines do not elaborate on further steps should diagnostic imaging be negative, yet testosterone levels remain markedly elevated. Selective venous sampling (SVS) from ovarian and adrenal veins has been performed sparingly to measure effluent androgen levels in both pre- and postmenopausal women.[3] However, there is debate on its utility to accurately localize a source of hyperandrogenism and, therefore, prompt management decisions. We report the case of an adolescent female with a presumptive diagnosis of PCOS and the diagnostic evaluation pursued, including SVS, to investigate her striking biochemical hyperandrogenism.

Case

A 12.7-year-old multiracial female was referred for evaluation of PCOS. Fourteen months post-menarche, she developed secondary amenorrhea, acne, hirsutism, and acanthosis nigricans. She had normal height and growth velocity, with a body mass index (BMI) greater than the 99th percentile. She was noted as Tanner stage 5 for breast and pubic hair. Black hair along the linea alba, lower back, upper lip, and chin was documented. No Ferriman-Gallwey score (FGS) was assigned. There was no clitoromegaly. Initial lab evaluation, detailed in Table 1, showed mild hyperandrogenism with total testosterone of 52 ng/dL (1.8 nmol/L), free testosterone of 1.3 ng/dL (0.05 nmol/L), and large ovarian volumes (left 15.6 mL, right 25 mL) on transabdominal ultrasonography (US). The patient was diagnosed with PCOS on the basis of the development of secondary amenorrhea (> 90 days between cycles more than 1 year post-menarche), presence of biochemical hyperandrogenism, and exclusion of other etiologies.[4] Immediate-release metformin (500 mg twice daily) was prescribed.

At follow-up at 13.9 years of age, she endorsed continued oligomenorrhea. Her obesity had worsened, and she noted a more muscular physique but denied worsening acne, hirsutism, male pattern hair loss, or clitoromegaly. Laboratory assessment revealed an increase in total and free testosterone to 158 ng/dL (5.5 nmol/L) and 3.6 ng/dL (0.12 nmol/L), respectively, and an increase in hemoglobin A1c (HbA1c) to 5.9% (Table 1). Because of the dramatic increase in testosterone, she underwent abdominopelvic magnetic resonance imaging (MRI), with no evidence of an ovarian or adrenal androgen-producing tumor. Again, the ovarian volumes were noted to be large (14.1 mL left, 15 mL

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Table 1
Timeline of Sequential Evaluations Listed by Patient Age*

Patient age (years)	Reference range	Baseline 12.7	13.9	14.3	14.5		14.9	15.3	15.6	15.9
Treatment at time of assessment			M	M COC	M COC		M TCP	M TCP	M TCP	TCP GLP1RA
Total testosterone (ng/dL)†	12-75 (12-16 y)	52	158	249	344		24	53	21	32
Free testosterone (ng/dL)†	<0.13-0.84 (12 y) <0.13-0.96 (13 y) <0.13-1.06 (14 y) <0.13-1.09 (15 y)	1.30	3.63	5.23	6.19		<0.04	1.06	0.17	0.16
Menstrual irregularity		X	X	X	X					
Weight (kg)		84.3	98.4	100.7	98	**Laparoscopic right oophorectomy**			92	
BMI z-score		2.42	2.54	2.56					2.28	
HbA1c (%)	4-6	5.6	5.9	5.2				5.1	5.0	5.0
FPG (mg/dL)	65-110	76	92	78	78			83	82	81
Fasting insulin (mcIU/mL)	2-18		74.3	48.2				16.8	20.4	16.7
DHEAS (mcg/dL)	0-149 (0-12 y) 30-550 (12-15 y)	137			238					
TSH (mcIU/mL)	0.35-5.5	4.22	7.55	5.29						
Transabdominal pelvic US‡		25 mL-R, 15.6 mL-L, no mass		5.2 mL-R, 8 mL-L, no mass						

COC, combined oral contraceptive; DHEAS, dehydroepiandrosterone sulfate; FPG, fasting plasma glucose; GLP1RA, GLP-1 receptor agonist; M, metformin; TCP, transdermal contraceptive patch; TSH, thyroid-stimulating hormone.
Reference ranges are taken from the reporting laboratory.

* Additional one-time laboratory assessments included 17-hydroxyprogesterone (51 ng/dL), beta-hCG (< 3 mIU/mL), estradiol (45 pg/mL), follicle stimulation hormone (4.8 mIU/mL), karyotype (46, XX), luteinizing hormone (3.5 mIU/mL), prolactin (15.4 ng/mL), sex-hormone binding globulin (22.9 nmol/L), tissue transglutaminase IgA (2.8 units), urine anabolic steroid screen (negative). These were all within the normal reference range based on female sex and age/Tanner stage.

† Total and free testosterone assay was performed at Mayo Clinical Laboratories (Rochester, MN) using liquid chromatography/tandem mass spectrometry (LC-MS/MS) and equilibrium dialysis/LC-MS/MS, respectively.

‡ Reported as ovarian volumes; R, right; L, left. Ovarian volumes were calculated using the ellipsoid formula of 0.523 × length (cm) × width (cm) × depth (cm).

right). Her metformin dose was increased to 1500 mg daily (switching to extended release). After progesterone-induced withdrawal bleeding, she began taking a cycled combined oral contraceptive (COC) with 0.03 mg of ethinyl estradiol and 0.15 mg of desogestrel. She was not interested in anti-androgen therapy (eg, spironolactone).

Six months later, at 14.3 years of age, total and free testosterone had increased to 249 ng/dL (8.6 nmol/L) and 5.23 ng/dL (0.18 nmol/L), respectively. She reported compliance with metformin but admitted she had only been taking her COC for 3 weeks before her visit. Her hirsutism had progressed, but no virilization developed. She had been amenorrheic for at least 4 months. Her metabolic parameters had improved, and her weight gain had slowed. Repeat transabdominal pelvic US showed normal ovarian volumes (left 8 mL, right 5.2 mL) and, again, no mass. Given the marked increase in testosterone, additional evaluations, including urine screen for anabolic steroids, karyotype, alpha-fetoprotein, and beta-hCG tumor markers, were conducted, which were all within expected limits. The patient denied intake of an interfering medication or supplement, such as biotin. Testosterone rose further to 344 ng/dL (11.9 nmol/L) despite 2 months of improved compliance with cycled COC (labs performed mid-pack) and metformin. She endorsed progressive hirsutism, voice deepening, and muscle mass accumulation. On physical exam, an increase in hair growth over the lower abdomen, lower back, chin, and sideburns was noted (no FGS recorded) and, again, no clitoromegaly. At this time, a trial of GnRH-agonist therapy was discussed with the patient and family. However, due to appropriate concern regarding the possibility of an occult androgen-producing tumor, it was decided that SVS be performed with interventional radiology.

Bilateral SVS was performed in interventional radiology via a right femoral vein access and approach. The bilateral gonadal and adrenal veins demonstrated typical anatomy. All 4 vessels were selectively sampled, and testosterone levels were analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Although more extensive steroid profiling (including provocative testing with hCG and/or adrenocorticotropic hormone) has been described with SVS,[5] due to consideration for patient cost, this was not performed.

Serum testosterone values from the venous sampling were 285 ng/dL (peripheral), 2300 ng/dL (right ovary), 203 ng/dL (left ovary), 224 (right adrenal), and 175 (left adrenal). These were consistent with a right-to-left ovary testosterone ratio of 11.3 and a right ovary-to-peripheral gradient of 8.1. She subsequently underwent an uncomplicated laparoscopic right oophorectomy. In contrast to the unilateral androgen source suggested by the SVS, pathology resulted in PCOS, with no evidence of a neoplasm. Grossly, the ovary measured 54 × 23 × 17 mm and weighed 12.8 gm. Serial sections every 4-5 mm revealed multiple fluid-filled cysts, measuring up to 7 mm in diameter. All sections were examined microscopically, confirming subcortical and deeper cysts (Fig. 1). The absence of a tumor on initial review by a pathologist prompted additional reviews, independently, by 3 pathologists, and all concurred with the initial findings. She continued metformin and, per patient preference, switched from COC to norelgestromin/ethinyl estradiol transdermal contraceptive patch (TCP). Fortunately, 3 months after the right oophorectomy, the patient exhibited normalization of testosterone levels, and her menstrual cycle resumed. She denied further increase in hirsutism, and acne improved. One year af-

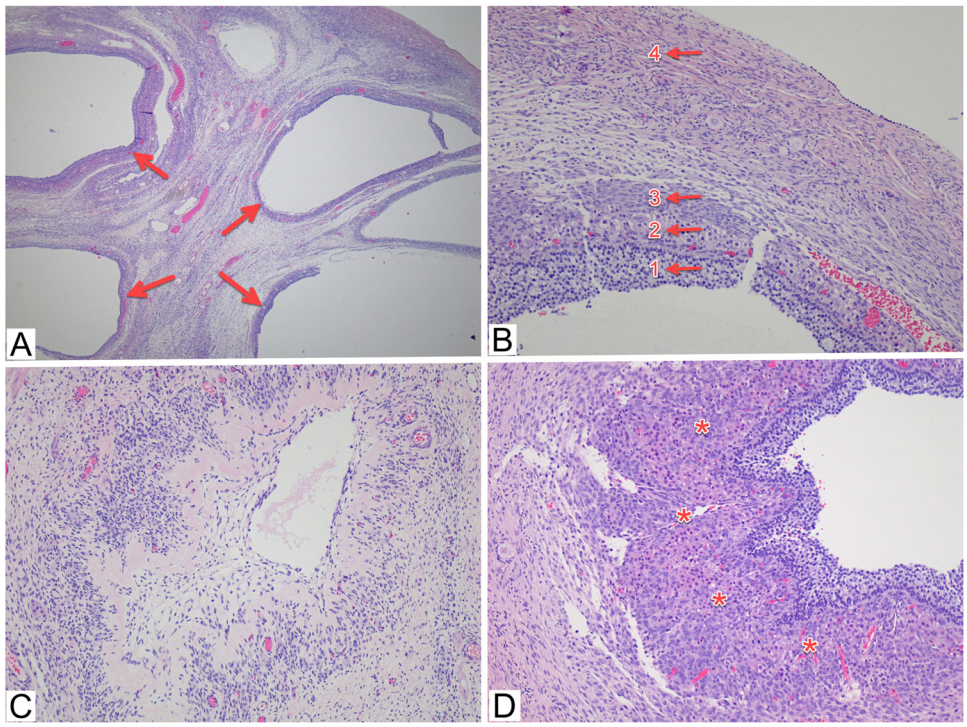

Fig. 1. Pathology sample of the right ovary which confirmed a diagnosis of polycystic ovary syndrome. (A) Cystic follicles, highlighted by arrows (H&E; 40×). (B) Cysts are lined by granulosa cells (arrow 1), luteinized theca interna (arrow 2), and theca externa (arrow 3).
Note: fibrotic superficial ovarian cortex (arrow 4). (H&E; 100×). (C) Collapsed atretic follicle (multilayered wall) simulating corpus albicans (H&E; 100×). (D) Follicular hyperthecosis (asterisks indicate layer of hyperplastic luteinized cells) (H&E; 100×). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ter the right oophorectomy, after losing nearly 9% of her body weight and her HbA1c reducing to 5.0%, she preferred to discontinue metformin and trial GLP-1 receptor agonist therapy (liraglutide) for her elevated BMI. Follow-up 2 months after metformin discontinuation, at age 15.9 years, her testosterone level and HbA1c continue to be normal on TCP and liraglutide.

Summary and Conclusion

Evaluation for PCOS requires exclusion of other etiologies of hyperandrogenism, including androgen-secreting tumors. This involves a detailed clinical history, physical exam, and biochemical androgen assessment.[1] The indications for radiological investigation of an androgen-secreting tumor include a total testosterone level greater than 150-200 ng/dL or a clinical presentation suggestive of rapidly progressive virilization (voice deepening, frontal balding, clitoromegaly) or defeminization (mammary atrophy.[1,2,6] However, when an androgen-secreting tumor is suspected, yet imaging is nondiagnostic, the ideal course of management for a hyperandrogenemic, premenopausal patient is not well established.

SVS from ovarian and adrenal vessels has been suggested as an alternative diagnostic approach to differentiate between unilateral and bilateral sources of hyperandrogenism when imaging results are nondiagnostic.[5,7] Moltz et al published a frequently cited study of SVS in 7 adult women and suggested that a unilateral ovary-to-peripheral gradient of greater than 2.7 in women with a peripheral testosterone level above 150 ng/dL was justification for surgical exploration.[5] More recently, a larger case series from Levens et al found a right-to-left ovarian testosterone ratio of greater than or equal to 1.44 to correctly identify right-sided neoplasms in 18 out of 20 women (90%) with a peripheral testosterone level above 130 ng/dL.[7]

However, there is still debate on the utility of sampling results to guide treatment decisions. Opponents propose that even if all vessels are successfully accessed, which can be challenging for even the most experienced centers, there is no consensus regarding the definition of a diagnostic testosterone gradient.[3] Some suggest that without a validated control substance (such as the use of cortisol with adrenal sampling to investigate hyperaldosteronism), the testosterone results are impossible to interpret. For example, a right-to-left gradient could simply be the result of more proximal vs distal catheter insertion or pulsatile secretion from the organ.[8]

Among pediatric females, there have been rare reports of the use of SVS to identify the source of hyperandrogenism. Both Levens et al[7] and Driano et al[9] published cases of 12-year-old females with severe hyperandrogenism who underwent right oophorectomy following SVS. The first patient demonstrated a right ovary-to-peripheral testosterone gradient of 4.0 and right-to-left ovary testosterone ratio of 3.8 and was ultimately diagnosed with PCOS.[7] The second patient with more impressive gradients of 19.0 (right ovary-to-periphery) and 27.2 (right-to-left ovary) was diagnosed with a right-sided ovarian steroid cell tumor previously unrecognized on imaging.[9] Of note, both patients had baseline peripheral testosterone levels of 150-

200 ng/dL and met the abovementioned SVS criteria for suggesting a unilateral lesion.[5,7] These cases highlight the challenge with interpreting SVS results in young females.

An additional option offered to our patient before SVS was a trial of GnRH agonist therapy. GnRH agonists have been utilized as a treatment modality in premenopausal women with severe ovarian hyperandrogenism unresponsive to traditional medical management, such as that seen with primary severe insulin resistance[10] or ovarian hyperthecosis.[11] However, improvement in hyperandrogenism with GnRH agonist therapy can be seen in ovarian neoplasms as well.[12] Thus, there is the possibility that a GnRH agonist could mask the clinical signs of an occult androgen-secreting tumor. Goyal et al reported this same consideration when evaluating severe hyperandrogenism in a 27-year-old female with a peak total testosterone of greater than 900 ng/dL (34.3 nmol/L) and nondiagnostic imaging.[11] Ultimately, SVS in their case demonstrated no testosterone gradient between the ovaries. As a result, their patient was treated with leuprolide and COC with dramatic improvement, therefore confirming a diagnosis of ovarian hyperthecosis. Considering our patient's desire to assess for a neoplasm more definitively, we similarly elected to first pursue SVS before consideration of GnRH agonist therapy.

With our patient's peripheral testosterone level of 344 ng/dL, SVS findings of a right ovary-to-peripheral testosterone gradient of 8.1, right-to-left ovary testosterone ratio of 11.3, and strong patient/parent desire for definitive therapy, laparoscopic right oophorectomy was performed. Pathologic results ultimately confirmed her to have PCOS, without evidence of neoplasm or hyperthecosis (Fig. 1). With the pathologic results indicative of PCOS, she continued her medical management after surgery. However, the patient preferred switching from COC to TCP at that time. Three months after unilateral oophorectomy, her signs and symptoms of PCOS improved, including normalization of her serum testosterone. Reassuringly, these improvements have persisted for over 12 months.

Although surgical management is clearly not standard of care for PCOS, particularly in youth, there are reports of unilateral oophorectomy resulting in improvements in menstrual regularity and biochemical hyperandrogenism in adult women with severe, treatment-resistant PCOS.[13] Why removal of a single ovary would be curative for a bilateral ovarian disease is not known, although it has been hypothesized that ovary-pituitary feedback in the remaining ovary could be altered, and/or simply removing a large amount of androgen-producing tissue could disrupt the pathophysiology of PCOS, thus allowing the remaining ovary to function normally.[13] Notably, because our patient switched from COC to TCP therapy immediately after right oophorectomy, it is possible that her clinical improvement is due to the impact of the TCP on her remaining ovary, rather than the unilateral oophorectomy itself.

In conclusion, we report the case of an adolescent female with striking biochemical hyperandrogenism (peak total testosterone of 344 ng/dL or 11.9 nmol/L) who underwent SVS in an effort to localize an androgen-producing tumor when radiologic imaging was nondiagnostic. Because of the marked elevation in baseline testosterone, patient/parent preference, and concerning testosterone gradients on venous sampling, she underwent unilateral oophorectomy. Although an androgen-secreting neoplasm was not identified, the removal of a single ovary has proven beneficial in treatment of her PCOS, with dramatic and persistent improvements in hyperandrogenism, menstrual irregularity, and insulin resistance.

Patient consent statement

Parental permission and patient consent for this report were obtained per the institution's ethical guidelines.

Disclosures

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