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Case Report

Ovarian Hyperthecosis in a 12-year-old Chinese Girl Presenting With Virilization

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Abstract

All girls presenting with virilization (which signifies severe hyperandrogenism) warrant thorough investigation. Ovarian hyperthecosis (OHT) is a rare cause of virilization in premenopausal women. Here, we report the case of a previously healthy 12-year-old Chinese girl with signs of virilization at puberty. Her serum total testosterone was elevated at 5.1 nmol/L (146.97 ng/dL) (normal: <1.4 nmol/L, <40.35 ng/dL). Workup for Cushing syndrome, sex development disorders, congenital adrenal hyperplasia, and adrenal and ovarian androgen-secreting tumors was unrevealing. Ovarian and adrenal venous sampling demonstrated ovarian hyperandrogenism without lateralization. Ovarian biopsy revealed nests of theca cells in the stroma of the right ovary, substantiating the diagnosis of OHT. A single dose of a GnRH analog resulted in the complete suppression of serum testosterone, supporting the diagnosis of OHT. Medical treatment with hormonal replacement therapy normalized serum testosterone levels. Our case report illustrates the diagnostic approach to virilization among girls at puberty and the diagnosis of OHT as the underlying pathology.

Key Words: ovarian hyperthecosis, virilization, hyperandrogenism

Abbreviations: 17-OHP, 17-hydroxyprogesterone; COC, combined oral contraceptive pill; CT, computed tomography; DHEA-S, dehydroepiandrosterone-sulfate; HRT, hormone replacement therapy; LDDST, dexamethasone suppression test; MRI, magnetic resonance imaging; OHT, ovarian hyperthecosis; PCOS, polycystic ovarian syndrome; USG, ultrasonography.

Introduction

Typical features of mild-to-moderate hyperandrogenism include hirsutism, acne, and oily skin. Virilization, which signifies severe hyperandrogenism, manifests as masculine habitus, androphonia, severe acne, and clitoromegaly [1]. Hyperandrogenism may be due to a high intake of exogenous androgens or androgen overproduction in the gonads or adrenal glands. The underlying pathologies include Cushing syndrome, congenital adrenal hyperplasia, sex development disorders, or androgen-secreting tumors [1].

In ovarian hyperthecosis (OHT), nests of luteinized theca cells are scattered ectopically throughout the ovarian stroma, resulting in LH-dependent ovarian hyperandrogenism [2]. The condition typically occurs in postmenopausal women and is driven by high levels of menopausal circulating LH or related to the "2-cell hypothesis," in which ovarian testosterone production by theca cells is uncovered in a postmenopausal woman by the loss of granulosa cell-mediated aromatization of testosterone to estradiol [2, 3]. It is a rare cause of ovarian hyperandrogenism in premenopausal women [2, 3]. Other differential diagnoses of hyperandrogenism should be excluded. The gold standard diagnostic modality is histopathology of the nests of luteinized theca cells in the ovarian stroma, and it is supported by marked elevations of serum testosterone levels from both ovaries (as demonstrated by ovarian venous sampling) and a >50% suppression of serum testosterone following a single dose of a GnRH analog [2, 3].

Case Presentation

A 12-year-old Chinese girl was referred to the endocrine clinic with androphonia for 2 years. She had thelarche, pubarche, and menarche at the ages of 11, 12, and 12.5 years, respectively. She experienced monthly menstruation for 4 months and then developed secondary amenorrhea. Her birth history, developmental history, and medical history were unremarkable. There was no history of breast atrophy, hyperpigmentation, or salt wasting. She was not on any medication and there was no family history of endocrine disease or sudden infant death. Her physical examination at presentation revealed a weight of 61.6 kg (1 kg above the 97th growth percentile), a height of 167.3 cm (5 cm above the 97th growth percentile; mid-parental height at the 90th growth percentile), and a body mass index of 22 kg/m^2 (90th-97th percentile) [4]. Nevertheless, her blood pressure was normal. She had androphonia and acne but no hirsutism, laryngeal prominence, or alopecia. Examination of the external genitalia revealed clitoromegaly, with her clitoris measuring 2.5 cm × 1.5 cm;

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however, the rest of her phenotype was feminine. She had no features of dysmorphism or Cushing syndrome. Systemic examination was normal with no palpable intra-abdominal or inguinal mass. Her pubertal stage was breast IV, pubic hair V, and axilla II per the Tanner staging.

Diagnostic Assessment

Her hormonal profile at presentation revealed elevated serum total testosterone (up to 5.1 nmol/L [146.97 ng/dL] [normal: <1.4 nmol/L, <40.35 ng/dL]). LH (2.0 IU/L), FSH (1.5 IU/L), and estradiol (107 pmol/L [29.15 pg/mL]) were within their respective pubertal ranges. Serum androstenedione (3.2 nmol/L [91.69 ng/dL] [normal: 0.7-6.0 nmol/L, 20.06-171.92 ng/dL]), dehydroepiandrosterone-sulfate (DHEA-S) (6.9 µmol/L [255.56 µg/dL] [normal: 0.9–7.6 µmol/L, 33.33-281.48 µg/dL]) and 17-hydroxyprogesterone (17-OHP) (2.1 nmol/L [normal: 0.6-4 nmol/L]) were normal. Tumor markers, including β-human chorionic gonadotropin (<2.0 IU/L [normal: <5 IU/L]), α-fetoprotein (<2.3 ug/L [normal: <8.8 ug/L]) and CA-125 (22 IU/mL [normal: ≤35 IU/mL]) were not elevated. The 24-hour urinary steroid profile and the standard-dose Short Synacthen test showed no evidence of congenital adrenal hyperplasia. Cushing syndrome was excluded by a normal 24-hour urinary free cortisol (81 nmol/day [normal: 24-140 nmol/day]) and an adequately suppressed cortisol level in the low-dose dexamethasone suppression test (LDDST) (from 311 nmol/L to <22 nmol/L [from 11.27 µg/dL to <0.8 µg/dL]). Serum total testosterone in LDDST was nonsuppressible (from 7.5 nmol/L to 10.7 nmol/L [from 216.14 ng/dL to 308.36 ng/dL]), supporting an extra-adrenal source of testosterone. Her karyotype was 46XX. Ultrasonography (USG) of the pelvic region revealed the pubertal appearance of the uterus and ovaries. Magnetic resonance imaging (MRI) of the abdomen and pelvis, including the bilateral ovaries and adrenal glands, was normal. 18F-fluorodeoxyglucose and 11 Choline-acetate positron emission tomography-computed tomography (CT) showed no abnormal metabolism at both adrenal glands or the adnexal region. Ovarian and adrenal venous sampling performed at the age of 13.7 years showed that the testosterone came from both ovaries without lateralization (serum free testosterone: left ovarian veins: 2152 pmol/L; right ovarian vein: 2719 pmol/L; left-to-right ratio: 1.26). Ovarian biopsy at the age of 13.9 years revealed nests of luteinized theca cells scattered within the ovarian stroma of the right ovary with no malignancy, and the left ovarian tissue was normal. The diagnosis of OHT was substantiated. A single dose of a GnRH analog (3.75 mg of leuprorelin acetate monthly depot subcutaneous injection) administered at the age of 14 years suppressed serum total and free testosterone by >50% and attained normalization (serum total testosterone from 1.7 nmol/L to 0.4 nmol/L [from 48.99 ng/dL to 11.53 ng/dL] [normal: <1.4 nmol/L, 40.35 ng/dL]) and free testosterone (from 51.7 pmol/L to 8.3 pmol/L [normal: <12.5 pmol/L]), supporting the diagnosis of OHT (Table 1).

Treatment

Hormone replacement therapy (HRT) was commenced at the age of 14.1 years. It comprised estradiol (2 mg daily on days 1-24 of each calendar month) and medroxyprogesterone acetate (5 mg daily on days 13-24 of each calendar month) and her monthly menstruation resumed. Partial suppression of serum free testosterone (14-22.4 pmol/L [normal: <12.5 pmol/L]) was achieved after 2 cycles of therapy. Estradiol (2 mg daily) was then given continuously on days 1 through 30 of each calendar month at the age of 14.3 years with the same regimen for medroxyprogesterone acetate. The complete normalization of serum free testosterone (8.3 pmol/L [normal: <12.5 pmol/L]) was achieved after 1 cycle of the new regimen (Table 2).

Outcome and Follow-up

On physical examination, her androphonia persisted but her clitoromegaly regressed partially. She continued to have monthly menstruation while on HRT.

Discussion

Here, we describe the case of a girl who presented with signs of virilization at puberty and had a >3-fold rise in serum total testosterone but had no history of exogenous androgen intake. The normal values of DHEA-S and 17-OHP suggested a gonadal rather than an adrenal source of testosterone [1]. Cushing syndrome was excluded because she did not have cushingoid features, her 24-hour urinary free cortisol levels were normal, and there was adequate suppression of cortisol in LDDST. The normal serum 17-OHP, 24-hour urine steroid profile, and standard-dose Short Synacthen test excluded congenital adrenal hyperplasia. MRI scans of the adrenal glands and ovaries did not reveal any adrenal or ovarian masses. Ovarian hyperandrogenism was suspected.

Ovarian theca cells produce dehydroepiandrosterone and androstenedione as a precursor to testosterone, which is the predominant androgen produced. Adrenal glands primarily produce DHEA-S and androstenedione, which undergo peripheral conversion to testosterone [2]. The differential diagnoses of ovarian hyperandrogenism include disorders of sex development, polycystic ovarian syndrome (PCOS), and ovarian androgen-secreting tumors but rarely OHT. Karyotype findings of 46XX excluded sex chromosome disorders. PCOS in adolescents typically presents with irregular menses or oligomenorrhea, mild-to-moderate biochemical and clinical hyperandrogenism, and USG may show a characteristic multifollicular appearance of ovaries [5]. Our patient presented with severe hyperandrogenism biochemically and clinically, which was atypical of PCOS. Radiological studies (including USG, CT, and MRI) may detect androgen-secreting tumors. Positron emission tomography-CT is reported to be more sensitive in detecting and localizing androgen-secreting tumors when conventional imaging is indistinctive. The 11 Choline-acetate tracer is preferable over 18F-fluorodeoxyglucose in detecting testosterone-producing ovarian tumors [6]. In our patient, imaging studies could not find a tumor; however, a small one could not be excluded. Testosterone is typically secreted from both ovaries in OHT whereas, in ovarian androgen-secreting tumors, the source lateralizes to the affected side. Venous sampling is an invasive procedure that requires expertise and should not be performed routinely [7]. In view of her atypical age for OHT and the remote possibility of an occult androgen-secreting tumor, ovarian and adrenal venous sampling was performed. An incidental finding was that our patient had 2 left ovarian veins (lateral and medial) and 1 right ovarian vein. Venous sampling revealed that testosterone originated

Table 1. Summary of the investigation results

Biochemical test	Results	Normal range
Total testosterone	**5.1 nmol/L (146.97 ng/dL)**	<1.4 nmol/L (<40.35 ng/dL)
Estradiol	107pmol/L (29.15 pg/ml)	
LH	2 IU/L	
FSH	1.5 IU/L	
Androstenedione	3.2 nmol/L (91.69 ng/dL)	0.7–6.0 nmol/L (20.06-171.92 ng/dL)
DHEA-S	6.9 µmol/L (255.56 µg/dL)	0.9–7.6 µmol/L (33.33–281.48 µg/dL)
17-OHP	2.1 nmol/L	0.6–4 nmol/L
β-HCG	<2.0 IU/L	<5 IU/L
AFP	<2.3 µg/L	<8.8 µg/L
CA-125	22 IU/ml	≤35 IU/ml
24 hours urine steroid profile	Normal	
SDSST	No evidence of CAH	
24 hours urinary free cortisol (nmol/day)	81 nmol/day	24–140 nmol/day
LDDST	Adequately suppressed cortisol from 311nmol/L to <22nmol/L (from 11.27 µg/dL to <0.8 µg/dL); **non-suppressible testosterone from 7.5 nmol/L to 10.7 nmol/L (from 216.14 ng/dL to 308.36 ng/dL)**	
Karyotype	46, XX	
Imaging	**Results**	
Pelvic USG	Pubertal appearance of the uterus and ovaries, no tumor	
Abdominal and pelvic MRI	Normal bilateral ovaries and adrenal glands, no tumor	
18 FDG and 11C PET CT	No abnormal metabolism at bilateral adrenal glands or adnexal region	
Ovarian and adrenal venous sampling	Ovarian origin without lateralization (Left to right ratio 1.26)	
Ovarian biopsy	Right ovary: nests of luteinized thecal cells scattered within the ovarian stroma; left ovary: normal left ovarian tissue	
GnRH agonist testing	>50% and normalization of serum total testosterone and free testosterone Serum total testosterone: from 1.7 nmol/L to 0.4 nmol/L [from 48.99 ng/dL to 11.53 ng/dL]; free testosterone: from 51.7 pmol/L to 8.3 pmol/L	

Abbreviations: LH, luteinizing hormone; FSH, follicle-stimulating hormone; DHEA-S, dehydroepiandrosterone-sulfate; 17-OHP, 17-hydroxyprogesterone; AFP, alpha-fetoprotein; SDSST, standard-dose Short Synacthen test; CAH, congenital adrenal hyperplasia; LDDST, low-dose dexamethasone suppression test; USG, ultrasonography; MRI, magnetic resonance imaging; 18 FDG, 18 F-fluorodeoxyglucose; 11C, 11Choline; PET-CT, positron emission tomography-computed tomography; GnRH, gonadotropin-releasing hormone

Table 2. Hormonal profiles after the commencement of hormone replacement therapy

	After the first cycle[a]	After the second cycle[a]	After the first cycle[b]	Normal range
Free testosterone	**14 pmol/L**	**22.4 pmol/L**	8.3 pmol/L	<12.5 pmol/L
Total testosterone	0.6 nmol/L (17.29 ng/dL)	0.9 nmol/L (25.94 ng/dL)	0.3 nmol/L (8.65 ng/dL)	<1.4 nmol/L (<40.35 ng/dL))

[a]Estradiol (2 mg daily on days 1-24) and Medroxyprogesterone acetate (5 mg daily on days 13-24) of each calendar month
[b]Estradiol (2 mg daily on days 1-30) and Medroxyprogesterone acetate (5 mg daily on days 13-24) of each calendar month

from both ovaries without lateralization as the interovary testosterone ratio was <1.4 [7]. Ovarian biopsy revealed nests of luteinized theca cells in ovarian stroma in the right ovary, which is diagnostic of OHT [2, 3]. A reduction of serum testosterone by >50% after a single dose of a GnRH analog injection, which indicates LH-dependent ovarian hyperandrogenism, supported the diagnosis of OHT [2, 3]. The majority of ovarian androgen-secreting tumors are LH-independent and cannot be suppressed by a GnRH analog. Nonetheless, there are a few reports of semiautonomous virilizing ovarian neoplasms that retained gonadotropin receptors and were suppressed by GnRH analogs [2, 3]. Regular ovarian imaging is deemed necessary in our patient.

PCOS and OHT differ in epidemiology, clinical features, biochemical findings, and underlying pathophysiology. PCOS is more common in adolescents and young women of reproductive age, whereas OHT is mainly reported in postmenopausal women [2, 3]. To the best of our knowledge, there is only 1 reported case of OHT in a premenopausal woman at the age of 27 years [8]. Most patients with PCOS have mild-to-moderate hyperandrogenism presenting with hirsutism, acne, and oligomenorrhea, whereas patients with OHT

typically present with virilization and secondary amenorrhea, signifying severe hyperandrogenism [2, 3]. A much higher androgen level is anticipated in OHT [2, 3]. In addition to an elevated serum total testosterone level, DHEA-S may also be elevated in PCOS [2, 3]. Radiologically, the sizes of the ovaries are increased in both PCOS and OHT. In PCOS, the ovaries are multifollicular. In OHT, ovaries are more solid in appearance, with bilateral increments in the ovarian stroma, and only occasional cysts are shown in severe cases [2, 3]. These features were not present in our patient. Histologically, active luteinized theca cells scatter throughout the ovarian stroma in OHT, whereas theca cells in PCOS are confined to areas around follicular cysts [2, 3].

There is limited experience in the management of OHT. Most postmenopausal women underwent bilateral oophorectomy. For those who are unfit or unwilling to undergo surgery, pharmacological treatment such as long-term GnRH analog therapy can be considered but with the concern of bone mineral density reduction [3]. Remission was reported after a course of GnRH analog therapy (intramuscular triptorelin acetate depot 3.75 mg every 28 days for 4 months) [9]. Antiandrogen therapy with either cyproterone acetate or spironolactone was reported as an alternative treatment option [10]. The experience of physicians in treating OHT in premenopausal women is even more limited. Combined oral contraceptive pills (COCs) (ethinyl estradiol 30 μg plus levonorgestrel 150 μg) were prescribed to a 27-year-old woman with OHT [8]. In our patient, options of COC and HRT were discussed. COCs are culturally not widely accepted among Chinese parents. The patient and her family opted for HRT for social reasons. HRT was commenced with estradiol (2 mg daily) on days 1 through 24 of each calendar month and medroxyprogesterone acetate (5 mg daily) on days 13 through 24 of each calendar month, with a drug-free period on days 25 through 30. Such a regimen only partially suppressed serum free testosterone levels after 2 cycles. Estradiol (2 mg daily) was then administered continuously on days 1 through 30 of each calendar month while keeping the same regimen for medroxyprogesterone acetate. The normalization of serum free testosterone was attained after 1 cycle of the new regimen.

To conclude, virilization in girls at puberty signifies severe hyperandrogenism and warrants thorough investigation. Androgen-secreting tumors should be excluded. Ovarian and adrenal venous sampling is only performed in inconclusive cases to demonstrate the source of hyperandrogenism. The gold standard diagnostic modality for OHT is histopathology of nests of luteinized theca cells in the ovarian stroma. A >50% suppression of serum testosterone following the administration of a single dose of a GnRH analog supports the diagnosis of OHT. Only a few studies on the treatment of OHT in premenopausal women are available in the current literature.

Learning Points

- Virilization in girls signifies severe hyperandrogenism and warrants thorough investigation to confirm biochemical hyperandrogenism, localize the source of androgens, and delineate the underlying pathology.
- Ovarian and adrenal venous sampling is only performed in inconclusive cases to identify the etiology of hyperandrogenism.
- The gold standard diagnostic modality for ovarian hyperthecosis is histopathology of nests of luteinized theca cells in the ovarian stroma. A >50% suppression of serum testosterone following a single dose of a GnRH analog supports the diagnosis of ovarian hyperthecosis.

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Contributors

All authors made substantial contributions to this manuscript. T.S.T.L. and L.M.W. were involved in the diagnosis of the condition, the management of this patient, and manuscript submission. E.W.Y.W. was involved in the diagnosis and management of this patient. H.F.H. was responsible for the patient's surgical operations. All authors have reviewed and approved the final draft of the manuscript.

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Original data generated and analyzed for this case report are included in this published article.

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