Case report

Severe hyperandrogenism due to ovarian hyperthecosis in a young woman

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Accepted 10 December 2019

SUMMARY

Hyperandrogenism is a relatively common clinical problem. However, severe hyperandrogenism causing virilisation is rare. A 27-year-old woman presented with generalised hirsutism, clitoromegaly, breast atrophy and secondary amenorrhoea. She had serum testosterone levels elevated to the adult male range. Administration of gonadotropin-releasing hormone (GnRH) analogue resulted in >50% suppression of serum testosterone which was suggestive of luteinising hormone-dependent ovarian hyperandrogenism. Imaging studies of abdomen and pelvis were normal, and ovarian venous sampling failed to show a gradient between the two sides. A presumptive diagnosis of ovarian hyperthecosis was, therefore, considered. Medical treatment with GnRH analogue and combined oral contraceptive pills was initiated to which an excellent clinical and biochemical response was noted. This case highlights a rare presentation of ovarian hyperthecosis in a young woman with severe hyperandrogenism mimicking a virilising neoplasm.

BACKGROUND

Hyperandrogenism is a relatively common problem that can negatively affect an individual's quality of life. Severe hyperandrogenism causing virilisation is, however, rare. Virilisation classically manifests as male pattern baldness, clitoral enlargement, deepening of the voice, undue muscular prominence and breast atrophy in a previously unaffected woman.[1 2] It is almost always associated with amenorrhoea, and its presence usually signals a serious underlying pathology (such as an androgen-producing neoplasm).

When evaluating a patient with severe hyperandrogenism, dynamic tests such as low-dose dexamethasone suppression test (LDDST) and gonadotropin-releasing hormone (GnRH) analogue suppression test are extremely helpful. On LDDST, normalisation or reduction of serum testosterone by >40% suggests non-tumorous hyperandrogenism (such as congenital adrenal hyperplasia), while a reduction of serum testosterone by >50% on GnRH analogue test is indicative of luteinising hormone (LH)-dependent ovarian hyperandrogenism (such as ovarian hyperthecosis).[3 4] Additionally, high-resolution cross-sectional imaging of abdomen and pelvis should be routinely obtained in a woman with serum testosterone >5.2–6.9 nmol/L or dehydroepiandrosterone sulfate (DHEAS) >19.0–21.7 μmol/L to exclude virilising ovarian or adrenal neoplasm.[5 6]

Ovarian hyperthecosis is a rare cause of severe hyperandrogenism. It manifests as LH-dependent functional ovarian hyperandrogenism and is characterised by the presence of nests of luteinised theca cells scattered throughout the ovarian stroma which secrete excess androgen.[7–9] This disorder has been mainly described in postmenopausal women, and its occurrence in younger age group is extremely rare. Our case highlights a rare presentation of ovarian hyperthecosis in a young woman with severe hyperandrogenism mimicking a virilising neoplasm.

CASE PRESENTATION

A 27-year-old unmarried woman presented to the endocrine clinic with complaints of increased growth of terminal, coarse and pigmented hair over the face, trunk and abdomen for the past 2 years. The patient also noted acneiform eruptions over the face and back, recession in the temporal hairline, increased size of clitoris and atrophy of both breasts over the past 1 year. She attained menarche at the age of 15 years and had regular cycles until a sudden cessation of menstrual cycles 6 months back. She denied the history of heaviness in voice or undue muscular prominence. There was no history of mucocutaneous hyperpigmentation, salt-wasting episodes, use of exogenous androgen or symptoms suggestive of Cushing syndrome/acromegaly. She was born of a non-consanguineous marriage with uneventful birth history, and none of the family members had a history of similar complaints. No family member had a history of diabetes mellitus.

Examination revealed a young, lean woman with a height of 162 cm, weight of 46 kg and body mass index of 17.5 kg/m^2. There were no clinical features of insulin resistance. She had generalised hirsutism with a modified Ferriman-Gallwey score of 20/36, multiple acneiform eruptions over face and back, receding temporal hairline, bilateral breast atrophy and clitoromegaly with the clitoral length of 15 mm and clitoral index of 45 mm^2 (>35 mm^2—abnormal). The rest of her general and systemic examination was unremarkable.

INVESTIGATIONS

Investigations (table 1) revealed an elevated adult male range serum testosterone (varying from 12.8 to 34.3 nmol/L), which failed to suppress on LDDST. Serum DHEAS, 17-hydroxyprogesterone (17-OHP) and plasma adrenocorticotropic hormone (ACTH) levels were normal, indicating the non-adrenal source of androgen excess. Next, she was worked

To cite: Goyal A, Malhotra R, Kulshrestha V, *et al*. *BMJ Case Rep* 2019;**12**:e232783. doi:10.1136/bcr-2019-232783

Table 1 Investigations of the patient at baseline

Parameter	Patient's value	Normal range/comments
Serum testosterone (08:00) (nmol/L)	12.8 22.8 34.3	0.28–1.67
Serum DHEAS (µmol/L)	2.70	2.66–9.23
Serum LH (IU/L)	2.1	2.4–12.6
Serum FSH (IU/L)	6.4	3.5–12.5
Serum fasting insulin (µIU/mL)	6.6	3.0–8.0
HOMA-IR	1.46	<2.0
Serum cortisol (08:00) (nmol/L)	234.5	171.0–535.2
Plasma ACTH (08:00) (pmol/L)	3.30	1.59–13.93
Post-LDDST cortisol (nmol/L)	18.2	<49.7
Serum T4 (nmol/L)	105.5	65.6–181.5
Serum TSH (mIU/L)	1.1	0.27–4.20
Serum prolactin (µg/L)	7.9	6.0–29.9
Serum 17-OHP (nmol/L)	1.3	<6.1
Post-LDDST testosterone (nmol/L)	17.4	No decline in serum testosterone from baseline
Postleuprolide (3.75 mg intramuscular) testosterone (nmol/L)	4.2	>50% decline in serum testosterone from baseline

ACTH, adrenocorticotropic hormone; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; HOMA-IR, homeostasis model assessment of insulin resistance; LDDST, low-dose dexamethasone suppression test; LH, luteinising hormone; 17-OHP, 17-hydroxyprogesterone; T4, thyroxine; TSH, thyroid-stimulating hormone.

up for a possible ovarian source of hyperandrogenism. Suppression test with leuprolide (3.75 mg intramuscular) revealed a more than 50% decline in serum testosterone (day 20), indicative of LH-dependent ovarian hyperandrogenism.

DIFFERENTIAL DIAGNOSIS

The differentials of severe hyperandrogenism in a young woman include neoplastic causes (such as virilising adrenal adenoma, adrenocortical carcinoma and virilising ovarian neoplasm), non-neoplastic causes (such as ovarian hyperthecosis and congenital adrenal hyperplasia) and iatrogenic androgen excess.

A possibility of adrenal source of hyperandrogenism was excluded with the findings of normal serum DHEAS concentration (elevated in adrenal adenoma, adrenocortical carcinoma and congenital adrenal hyperplasia), normal suppression of serum cortisol on LDDST (adrenocortical carcinoma often cosecrete glucocorticoids and sex steroids), normal serum 17-OHP concentration (elevated in congenital adrenal hyperplasia and rarely adrenocortical carcinoma) and failure of serum testosterone to suppress on LDDST (suppression is expected in ACTH-dependent hyperandrogenism due to congenital adrenal hyperplasia).[10–13] The patient denied a history of iatrogenic androgen administration, and serum gonadotropin concentrations were not suppressed, making iatrogenic androgen excess unlikely. GnRH agonist suppression test revealed >50% suppression of serum testosterone, which suggested LH-dependent ovarian hyperandrogenism. Imaging studies (ultrasonography pelvis and CT of abdomen and pelvis) did not reveal any mass lesion in bilateral ovaries. To conclusively exclude the possibility of an ovarian neoplasm, she was subjected to ovarian venous sampling (OVS). It failed to show any gradient between the two ovaries, suggestive of bilateral androgen overproduction. A presumptive diagnosis of severe functional ovarian hyperandrogenism due to ovarian hyperthecosis was therefore considered.

TREATMENT

A single dose of GnRH analog-leuprolide acetate depot injection (11.25 mg intramuscular) was administered 1 day before her hospital discharge. Because suppression of pituitary gonadotropins is expected with GnRH analogue therapy, combined oral contraceptive pills (COCPs) (ethinyl estradiol 30 µg+levonorgestrel 150 µg) were added to her treatment regimen for withdrawal bleeding. She was explained about the treatment latency in terms of benefit in hirsutism and advised to undergo cosmetic interventions in the interim period.

OUTCOME AND FOLLOW-UP

At a follow-up visit 3 months later, testosterone declined to 1.2 nmol/L (N: 0.28–1.67 nmol/L). She was advised to continue COCP therapy alone. On subsequent follow-up visits (at 6 and 9 months), she reported regular withdrawal bleed and continued to have normal serum testosterone levels (0.7 and 1.1 nmol/L, respectively). A significant improvement in the physical manifestations of hyperandrogenism–hirsutism, acneiform eruptions, temporal hairline recession and breast atrophy was also noted at the end of 1 year.

DISCUSSION

Ovarian hyperthecosis is usually described as an extreme form of polycystic ovary syndrome (PCOS), which presents with signs and symptoms of severe hyperandrogenism. The disorder shares its pathophysiology with PCOS in that both functional ovarian hyperandrogenism and insulin resistance contribute to the androgen excess state. However, unlike PCOS where theca cells are confined to the area around cystic follicles, nests of luteinised theca cells are scattered throughout the ovarian stroma in hyperthecosis, contributing to the high androgen levels usually seen.[8 14] Ovarian hyperthecosis is seen primarily in postmenopausal women; its occurrence in women of reproductive age group is extremely rare.[15] Treatment involves the use of GnRH agonists in young women of reproductive age group. On the other hand, bilateral oophorectomy is preferred in postmenopausal women, with GnRH agonists reserved for those not ready or fit for surgery.[16 17]

Our patient presented with features of virilisation with markedly elevated serum testosterone levels, suspicious for a neoplastic pathology. Dynamic testing revealed >50% reduction of serum testosterone following GnRH analogue administration (suggestive of LH-dependent ovarian hyperandrogenism), while imaging of abdomen and pelvis did not reveal a mass lesion in bilateral ovaries. A virilising ovarian neoplasm is expected to show an unsuppressed testosterone response to the GnRH analogue suppression test. However, few cases of semiautonomous virilising ovarian neoplasm which continue to retain gonadotropin receptors and show suppression in response to GnRH analogues have been described in the literature.[18–21] Keeping this in mind, a decision to carry out OVS was taken. OVS failed to show any gradient between the two sides, favouring a diagnosis of ovarian hyperthecosis. A remarkable clinical and biochemical response to treatment with GnRH analogue (leuprolide acetate) and COCPs further confirmed the diagnosis. The remarkable absence of features of insulin resistance and excellent response to treatment with COCP therapy was noteworthy in this case. As suggested previously, only a moderate suppression of gonadotropins (achieved with COCPs) may be sufficient to maintain

normal androgen levels in patients with functional ovarian hyperandrogenism.[22]

To conclude, ovarian hyperthecosis may present with severe hyperandrogenism in young women, mimicking a virilising neoplasm. This case highlights the importance of careful history and physical examination along with a meticulous stepwise investigative approach (including the use of dynamic tests, venous sampling and imaging procedures) in approach to a patient with severe hyperandrogenism.

Learning points

- The presence of virilisation in a woman usually indicates a serious underlying pathology, warranting detailed evaluation.
- Imaging of abdomen and pelvis should be obtained in those with serum testosterone >5.2–6.9 nmol/L or serum dehydroepiandrosterone sulfate >19.0–21.7 µmol/L to exclude a virilising neoplasm.
- Dynamic tests such as low-dose dexamethasone suppression test and gonadotropin-releasing hormone analogue suppression test are useful in the evaluation of patients with severe hyperandrogenism.
- Ovarian hyperthecosis is cause of luteinising hormone -dependent ovarian hyperandrogenism. It is characterised by the presence of nests of luteinised theca cells scattered throughout the ovarian stroma which secrete excess androgen.
- This disorder has been described mainly in postmenopausal women. However, rarely, it may manifest in young women, mimicking a virilising ovarian neoplasm.

Acknowledgements The authors thank Dr Pramila Dharmshaktu and Dr Rajesh Khadgawat (Department of Endocrinology, AIIMS, New Delhi), Dr Devasenathipathy Kandasamy (Department of Radiodiagnosis, AIIMS, New Delhi) and Dr Alka Kriplani (Department of Obstetrics and Gynecology, AIIMS, New Delhi) for their help in managing the patient.

Contributors AG and RM diagnosed and managed the patient, carried out a literature search, collected data about the case and drafted the manuscript. VK and GK helped in patient management and edited the manuscript. All authors approved the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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