Rare disease

Virilising ovarian tumour in a woman with an adrenal nodule

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Androgen secreting tumours are the least commonly encountered androgen excess disorders, having a prevalence of 0.2%. Androblastomas of the ovary comprise less than 0.5% of all ovarian tumours. Pure Leydig cell tumours are very rare and almost always show secretion of male sex hormones.

A 41-year-old multipara Filipino woman presented with a 2-year history of amenorrhoea and virilisation characterised by hirsutism, androgenic alopecia, masculine habitus and clitoromegaly. Diagnostic evaluation showed markedly elevated serum testosterone and normal dehydroepiandrosterone sulfate. Normal ovaries were seen on initial transvaginal ultrasound. A low dose dexamethasone suppression test suggested an ovarian source. A left adrenal nodule was seen on CT scan. Doppler transvaginal ultrasound revealed a solid lobulated structure in the right ovary. The patient underwent surgery and histopathology showed a Leydig cell tumour, hilar type. Serum testosterone levels normalised 3 days after surgery.

Specific clinical and biochemical investigation of androgen secreting neoplasms is very important for correct diagnosis of these rare tumours.

BACKGROUND

Androgen secreting tumours are generally associated with rapidly progressive symptoms of hyperandrogenism resulting in virilisation. They are the least common of the androgen excess disorders, having a prevalence of 0.2%.^{1 2}

These tumours may arise from the adrenal glands or the ovaries. Androblastomas of the ovary may present as

tumours of Sertoli cells and/or Leydig cells (most often in combination) and comprise less than 0.5% of all ovarian tumours.^{3 4} Pure Leydig cell tumours are very rare and almost always show secretion of male sex hormones. Over 80% are associated with defeminisation or frank virilisation.⁴

Figure 1 Marked frontotemporal balding/androgenic alopecia.

Figure 2 The patient showing male habitus.

We consider in detail the causes of hyperandrogenism and their specific clinical and biochemical expressions. Moreover, we also discuss the metabolic sequelae because these patients are at increased risk for cardiovascular atherogenic complications.

CASE PRESENTATION

A 41-year-old multipara Filipino woman, with a 5-year history of hypertension, was referred to Philippine General Hospital because of virilisation. Two years previously she had noted progressive hair growth and coarseness of hair over her arms, legs, chest, back, thighs and abdomen. She also developed facial hair which prompted her to shave three times a week initially and then daily thereafter. Male pattern baldness, the development of a male habitus, weight gain, increased libido, decreased breast size and

clitoromegaly were also noted (figure 1-3). At this time, she was also diagnosed with type 2 diabetes mellitus based on elevated fasting blood sugar levels during a routine check-up at work. She took glibenclamide for a year. She also developed periodontitis manifesting as loosening of teeth a few months prior to her consultation. At this time, there was documented hyperglycaemia, glucosuria, albuminuria and dyslipidaemia. She was started on metformin, glibenclamide, simvastatin and losartan.

The family medical history revealed that both parents had diabetes and hypertension.

Menarche was at age 14 with regular monthly periods until 1 year prior to consultation when her menses stopped. She had three previous pregnancies, the first and third children were born via normal spontaneous delivery in 1989 and 1993, respectively, with estimated birth weight of 6 lb

Figure 3 Pelvic examination revealed external genitalia typical of an adult female but with clitoromegaly.

Table 1 Laboratory examination results

Test	Result	Normal range
Prolactin (mIU/l)	311.7	90–500
8:00 h Serum cortisol (nmol/l)	182.2	154–638
17-Hydroxyprogesterone (OHP) (nmol/l)	11.6	0.5–3.3 (follicular) 2.1–9.4 (luteal) 0.24–3.9 (post menopausal)
Testosterone (nmol/l)	63.3	0.9–4.5
DHEAS (μmol/l)	3.9	0.24–6.37
TSH (μIU/ml)	0.764	0.27–4.2
FT4 (pmol/l)	18.30	12–22

DHEAS, dehydroepiandrosterone sulfate; FT4, free thyroxine; TSH, thyroid stimulating hormone.

Table 2 Special tests

	Before	After
Dexamethasone suppression test		
Testosterone (nmol/l)	137.7	133.7
Cortisol (nmol/l)	100.5	9.4
DHEAS (μmol/l)	4.0	1.5
ACTH stimulation test		
17-Hydroxyprogesterone (OHP) (nmol/l)	11.6	12.8
Cortisol (nmol/l)	165.5	605.8

ACTH, adrenocorticotrophic hormone; DHEAS, dehydroepiandrosterone sulfate.

Figure 4 Abdominal CT scan showed an isodense nodule located in the medial left adrenal gland measuring approximately 1×1.5 cm.

Figure 5 Doppler transvaginal ultrasound revealed a $3.7 \times 2.5 \times 2.2$ cm solid lobulated structure in the right ovary with low resistance indices.

Figure 6 The right ovary had changed into a unilocular solid mass measuring 4×2.5×2 cm. The mass was firm and highly vascular.

and the second pregnancy was a blighted ovum. She has been on contraceptive pills for 13 years (ethinyl oestradiol, norgestrel and ferrous fumarate) and her last intake was 6 months prior to consultation.

On physical examination, she had a body mass index of 28.9 kg/m². Her blood pressure was 160/100 mm Hg. She had androgenic alopecia and a male habitus. Hair was present over the upper lip, sideburns, chin, chest, upper back, abdomen, arms, thighs, legs and sacral area. Her modified Ferriman-Gallwey score was 25. She did not have moon facies, buffalo hump, acanthosis nigricans, anterior neck mass or breast discharge. Abdominal circumference measured between the iliac crest and the lowest rib was 87 cm. There were whitish abdominal striae. Except for the presence of an enlarged clitoris, the pelvic examination did not reveal any masses or tenderness.

INVESTIGATIONS

Hormonal evaluation showed normal serum prolactin, free thyroxine, thyroid stimulating hormone and 8:00 h cortisol.

Serum total testosterone was markedly elevated suggesting an androgen secreting neoplasm (ASN). Dehydroepiandrosterone sulfate (DHEAS) was normal which argued against an adrenal source. As 17-hydroxyprogesterone (OHP) was 11.6 nmol/l, an adrenocorticotrophic hormone (ACTH) stimulation test was carried out to ascertain non-classical adrenal hyperplasia (NCAH). This showed a value of 12.8 (less than 30–36 nmol/l) ruling out NCAH (tables 1, 2).

A low dose dexamethasone suppression test showed non-suppressed testosterone levels and suppressed cortisol and DHEAS levels, suggesting an ovarian source.⁵

Table 3 Investigations for the adrenal nodule

Test	Result	Normal value
24 h Urine metanephrine	0.79	<1 mg/24 h
Serum aldosterone	28.30	Supine 1.73–37.22 ng/ml
Plasma renin activity	0.18	Supine 0.5–1.9 ng/ml/h

The first transvaginal ultrasound showed normal ovaries. Abdominal CT scan showed an isodense nodule located in the medial left adrenal gland measuring approximately 1×1.5 cm (figure 4). The left ovary was not well visualised, while the right ovary was not enlarged and did not abnormally enhance.

Since there was still a strong suspicion that this was ovarian in origin, we referred the patient to the gynaecology service. Doppler transvaginal ultrasound confirmed our suspicion and revealed a 3.7×2.5×2.2 cm solid lobulated structure in the right ovary with low resistance indices (figure 5; table 3).

DIFFERENTIAL DIAGNOSIS

Our differential diagnosis based on the history and physical examination in this case is described below.

Androgen secreting neoplasm

The rapid progression of hirsutism and evidence of virilisation are highly suggestive of an ovarian or adrenal tumour. Secondary amenorrhea accompanied by virilisation after discontinuation of oral contraceptives is clinically suggestive of an ovarian source. Such symptoms can be masked by the use of oral contraceptives which may also decrease androgen secretion by the ovarian tumour.⁶

Figure 7 On cut section, $\frac{3}{4}$ of the right ovary was noted to be a brownish, necrotic, firm lobulated mass.

Figure 8 Leydig cell tumour, hilar type. The tumour is composed of cells with abundant eosinophilic cytoplasm (A, lower left) or with abundant intracytoplasmic lipid (B, lower right). Note the characteristic Reinke crystal (centre).

Figure 9 Leydig cell tumour, hilar type. This tumour is well circumscribed. Note its location as regards the ovarian hilar vessels (H&E $\times 40$).

Hyperthecosis

Ovarian stromal hyperthecosis is usually characterised by a long history of anovulation, amenorrhea and slowly but relentlessly progressing virilisation. In perimenopausal women and women of reproductive age, symptoms of hyperthecosis may be of rapid onset, while androgen producing tumours characteristically cause rapidly progressing signs of androgen excess.⁷

Postmenopausal virilisation can indicate ovarian hyperthecosis. Clinical imaging can help detect hyperthecosis, which causes hirsutism.

Non-classical adrenal hyperplasia

No symptom of hyperandrogenism is specific to NCAH, so the clinical presentation cannot be used for the diagnosis of NCAH. Clitoromegaly, male habitus and temporal baldness are infrequent findings unless the patient has undiagnosed simple virilising CAH. Recent data from a multicentre study including 220 patients suggested that it is a progressive disorder, with the degree of hirsutism increasing with the patient's age. It should also be remembered that many women with NCAH conceive spontaneously.⁸

Drug induced hyperandrogenism

Many drugs can induce hyperandrogenic signs and symptoms including hirsutism, acne, seborrheic dermatitis, male pattern baldness, menstrual irregularity, clitoral hypertrophy or deepening of the voice. The principal mechanisms resulting in drug induced hyperandrogenism are either an increase in circulating androgen levels or an intrinsic activity of the drug.⁹

Our patient has been on oral contraceptive pills (OCP) for 13 years. She was taking an OCP composed of norgestrel, ethinyl oestradiol and ferrous fumarate. Norgestrel,

Table 4 Patient's weight, BMI and abdominal circumference

	June 2009	August 2009	September 2009
Weight (kg)	66.65	60.6	55
BMI (kg/m ²)	28.85	24.44	22.18
Abdominal circumference (cm)	87	82	72

BMI, body mass index.

Table 5 FBS, lipid profile, HbA1c and urinalysis results

	On initial consult	August 2009	Sept–October 2009
FBS (mg/dl)	206.63	107.82	107.04
2-h post prandial	231.92		175.1
Lipid profile			
Cholesterol	281.14	223.55	147.5
Triglycerides	88.50	107.97	103.8
HDL	49.42	49.42	64.48
LDL	215.06	152.51	61.8
HbA1c			6.9%
Urinalysis	Trace albumin (+) sugar	(–) Albumin (–) sugar	(–) Albumin (–) sugar

FBS, fasting blood sugar; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

which is a synthetic progestin, has attenuated androgenic properties. Synthetic progestins have the ability to bind to the androgen receptor directly inducing androgenic effects and they lower sex hormone-binding globulin and bind to it, displacing testosterone and increasing levels of free active testosterone.⁹

In our patient, the appearance of symptoms after discontinuation of the OCP makes this diagnosis unlikely. In addition, the incidence of hyperandrogenism is low because the ethinyl oestradiol content of the pill attenuates

the androgenic effects of progestins.⁹ Contraceptives which only contain progestins have a higher prevalence of androgenic side effects.

Hyperandrogenism and metabolic syndrome

The metabolic sequelae of hyperandrogenaemia are evident in this case. These are a major consideration as they place patients at increased risk for later cardiovascular complications. Our patient had abdominal obesity, overt type 2 diabetes mellitus, hypertension and dyslipidaemia. The metabolic parameters improved with removal of the source of hyperandrogenism.

TREATMENT

Surgery

The patient subsequently underwent exploratory laparotomy. The following procedures were carried out: peritoneal fluid cytology, total hysterectomy with bilateral salpingo-oophorectomy, infracolic omentectomy, random peritoneal biopsy, bilateral lymph node dissection and para-aortic lymph node sampling.

Intraoperative findings showed that the right ovary was a unilocular solid mass measuring 4×2.5×2 cm. The mass was firm and highly vascular. On cut section, ¾ of the right ovary was noted to be a brownish, necrotic, firm lobulated mass. The left ovary was smooth, nodular and pearly white, measuring 2×1.5×1.0 cm (figure 6-7).

There was no ascites. The liver, subdiaphragmatic surface, gallbladder, spleen, kidneys, intestines, omentum and appendix were smooth and grossly normal. Two nodes at the iliac portion were noted to be enlarged. The remainder of the abdominopelvic organs were grossly normal.

OUTCOME AND FOLLOW-UP

The patient tolerated the surgery well. On her third post-operative day, serum testosterone was normal (1.8 nmol/l). Three months after surgery, her serum testosterone level was down to 0.64 nmol/l.

Histopathological findings showed a 5×3×2 cm right ovary with an attached fallopian tube measuring 5×0.4 cm. Cut section of the ovary revealed a 3×2×2 cm well defined, cream/tan-coloured mass. Serial sections of the mass revealed a lobulated cut surface.

The final histopathological diagnosis was Leydig cell tumour, hilar type, with crystals of Reinke, ovary, right. Specimen labelled right paracolic gutter was noted to be positive for tumour (figure 8-9).

The patient was diagnosed with hilar Leydig cell tumour with positive metastases to the paracolic gutter (ovarian cancer stage IIIC). She is at present receiving adjuvant chemotherapy with bleomycin, etoposide and cisplatin.

Metabolic parameters

Around the time that her symptoms of virilisation started, the patient was diagnosed with diabetes and dyslipidaemia. Eventually she was diagnosed as having metabolic syndrome based on the presence of abdominal obesity, diabetes mellitus, hypertension and low *high-density lipoprotein*.

Upon follow-up, there was decreased weight and abdominal circumference and noted improvement in metabolic parameters (tables 4, 5).

DISCUSSION

Assessment of a patient with suspected hyperandrogenism should include serum testosterone, 17-OHP and DHEAS. Evaluation of androgen levels and their site of secretion is essential. Other endocrine studies as suggested by the history and physical examination, are also warranted.⁵

Testosterone

Excess androgen may originate from either an adrenal or an ovarian tumour. Both sources may produce elevated testosterone levels. A combination of plasma testosterone concentration greater than 200 ng/dl (8.7 nmol/l) (or two to three times the upper normal range) with a normal DHEAS level is highly suggestive of an ovarian ASN. A combined increased testosterone concentration greater than 200 ng/dl (8.7 nmol/l) with an elevated DHEAS level of more than 600 µg/dl (16.3 µmol/l) is highly suggestive of an adrenal ASN.⁶

With reference to two studies of extensive clinical experience of hyperandrogenism, the different aetiologies of hyperandrogenism other than those secondary to ASNs, did not have serum testosterone levels comparable to the values seen in our patient. NCAH patients displayed the highest testosterone levels in the study by Carmina *et al* with mean values of 3.88±1.04 nmol/l (112±30 ng/dl) and patients with hyperandrogenic insulin resistant acanthosis nigricans (HAIRAN) syndrome displayed the highest testosterone levels in the study by Azziz *et al* showing mean values of 4.08±4.74 nmol/l (111.91±136.72 ng/dl).^{1 2} Our patient's serum testosterone level was as high as 137.7 nmol/l, which was highly suggestive of tumoural origin.

17-OHP and ACTH stimulation for NCAH

A basal screening level of 17-OHP of more than 2–4 ng/ml (6–12 nmol/l) mandates an ACTH stimulation test to confirm the diagnosis. A post ACTH stimulation 17-OHP level of 10–12 ng/ml (30–36 nmol/l) is consistent with the diagnosis of NCAH, although some authors suggest a higher cut-off of 20 ng/ml (60 nmol/l).^{10 11}

As our patient's initial 17-OHP was 11.6 nmol/l, we proceeded with an ACTH stimulation test which showed a post stimulation level of 12.8 nmol/l. False positive results (ie, elevated levels) may be observed in patients with androgen secreting tumours as well.⁸

Dehydroepiandrosterone sulfate

Despite the initial findings of normal ovaries on the first transvaginal ultrasound and a left adrenal nodule on abdominal CT scan, we pursued our search for an ovarian cause because of the presence of normal serum DHEAS. This was also supported by our findings in the low dose dexamethasone suppression test. We decided to refer this patient to the gynaecology service who carried out a Doppler transvaginal ultrasound which detected the presence of a small solid ovarian tumour confirming our initial impression.

Low dose dexamethasone suppression test

We followed the 2-day adrenal suppression test using 0.5 mg dexamethasone tablets as specified in the American Association of Clinical Endocrinologists (AACE)

Hyperandrogenism Guidelines. The testosterone level failed to be suppressed but the DHEAS and cortisol responded, pointing to an ovarian source.⁵

However, in a study by Kaltsas *et al*, it was concluded that the utility of this test is in distinguishing androgen secreting tumours from non-tumorous hyperandrogenism by demonstrating lack of testosterone suppression in tumoural causes which is associated with 100% sensitivity and 88% specificity.¹²

Leydig cell tumour

Most androgen secreting ovarian tumours are sex cord stromal tumours (SCST) which comprise less than 5% of all ovarian malignancies.¹³ Only about 3% of SCST are Sertoli-Leydig cell tumours (SLCTs), in which the components to a greater or lesser extent recapitulate the cells of the testis at various stages of development.^{3,4} SLCTs consist of Sertoli cells only, Leydig cells only or a combination of both. They were originally termed either 'androblastomas' or 'arrhenoblastomas' so as to carry the connotation of masculinisation, and account for less than 0.5% of all ovarian tumours.³

Pure Leydig cell tumours account for 0.1% of all ovarian tumours.⁷ They are categorised as either hilar or non-hilar Leydig cell tumours. In our patient, the virilising tumour was a hilar cell tumour. Such tumours are generally benign, small (<4 cm) and unilateral. They are solid, fleshy and well circumscribed and appear yellow, orange or more commonly brownish in colour. Crystals of Reinke, which must be seen to classify the tumour as Leydig cell, are elongated, hexagonal eosinophilic crystals present in the cytoplasm or rarely in the nucleus.¹³ These were present in our patient.

Imaging may miss these tumours due to their small size and they are often embedded within the ovary.⁷ They may be difficult to identify on radiological imaging, in part because they are isoechoic to the uterus on ultrasound and isoattenuating on CT scan. Small steroid cell tumours have been described as slightly hypoechoic or hyperechoic (compared to the ovary) with high diastolic flow on Doppler interrogation. Our patient's ultrasonogram and CT scan failed to detect the presence of a solid ovarian mass, which was only identified on Doppler interrogation.

Review of the local literature found only two case reports on ovarian virilising tumours, which were diagnosed at a reproductive age of 24 and 26 years. Histopathology revealed lipid cell tumour and Sertoli-Leydig cell tumour.^{14,15} The presence of an adrenal nodule on CT scan does not rule out an ovarian androgen secreting tumour.¹⁶ To our knowledge, this is the first local case report of a pure Leydig cell tumour.

Learning points

- ▶ Specific clinical and biochemical investigation of androgen secreting neoplasms is very important for correct diagnosis of these rare tumours.
- ▶ A high index of suspicion is warranted because androgen secreting ovarian tumours may be missed because of their small size.
- ▶ Transvaginal ultrasound with Doppler is helpful in the detection of these tumours.
- ▶ An adrenal nodule on CT scan does not rule out an ovarian androgen secreting tumour, so it is necessary to correlate biochemical findings with the results of imaging tests.
- ▶ The metabolic sequelae of hyperandrogenism are of major importance because they place patients at increased risk for later cardiovascular complications.

Competing interests None.

Patient consent Obtained.

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