Case report

Adrenocortical carcinoma: an ominous cause of hirsutism

Suhaib Radi 1, Michael Tamilia2

SUMMARY

Hirsutism is a common medical presentation to family physicians, internists and endocrinologists. Although the cause is commonly benign, a more serious or life-threatening one should not be missed. Here we report a 58-year-old woman, assessed for hirsutism and 15-pound weight gain, with associated easy bruising and mood swings. On physical examination, she was hypertensive with central obesity. Laboratory work was significant for erythrocytosis, leukocytosis with lymphopenia and transaminitis. With this initial clinical picture, a provisional diagnosis of cortisol and androgen hypersecretion was suspected. Further investigations revealed non-suppressible early morning cortisol and low-dose dexamethasone, elevated 24 hours urinary-free cortisol and late night salivary cortisol. In addition, serum adrenocorticotropic hormone was low and androgens were elevated. These results supported the provisional diagnosis and imaging of the adrenals showed a large 10.4×7.7×5.2 cm right adrenal mass, consistent with adrenocortical carcinoma, for which she underwent surgical resection.

BACKGROUND

Hirsutism is a fairly common medical problem that affects millions of women around the world, and can cause a significant psychological burden. It is defined as an unwanted androgen-dependent hair growth in females, that is on the face, chest and back, which differentiates it from hypertrichosis, a diffuse hair growth.1 There are many causes of hirsutism, most of which are benign, and polycystic ovary syndrome (PCOS) is the cause in 3 out of 4 hirsute women.2 However, the aetiology sometimes can be life-threatening, and early detection and treatment is key to avoid detrimental consequences. Table 1 summarises the causes of hirsutism and differentiating features for each one. In this report we present a life-threatening cause of hirsutism, with elaboration on clinical features to differentiate benign causes of hirsutism from those with dire consequences.

CASE PRESENTATION

A 58-year-old woman was assessed for hirsutism and a 15-pound weight gain over 1 year despite strict dieting and regular exercise. Her previous medical history was significant for hypertension, dyslipidemia, hypothyroidism and remote hysterectomy for fibroids. Her medications included amiodipine, perindopril, furosemide, fluvastatin and desiccated thyroid extract. The review of systems revealed complaints of tiredness, insomnia, loss of scalp hair, easy bruising and mood swings. She first noticed the weight gain and alopecia 12 months ago, but her symptoms progressed more rapidly over the last 4 months. On physical examination, the blood pressure was 152/98 mm Hg, and the body mass index (BMI) 30.8 kg/m2 with abdominal distribution of the adiposity. There was mild facial acne, sparse terminal hairs on the chin and some thinning of scalp hair. Her Ferriman-Gallwey scale for hirsutism was 11, indicating mild degree of hirsutism. On further inspection, there were isolated forearm bruises and pearl-coloured stretch marks on her abdomen.

INVESTIGATIONS

The initial blood work revealed an elevated haemoglobin of 172 (N: 120–152 g/L), white blood cells of 12 (N: 4–11×10^9/L), with lymphopenia of 0.7 (N: 1.2–3.5×10^9/L), an elevated alanine aminotransferase of 238 (N: 5–40 U/L) and lactate dehydrogenase of 818 (N: 110–220 U/L). The remaining liver profile, the glycated haemoglobin A1c and the serum electrolytes including potassium were normal.

DIFFERENTIAL DIAGNOSIS

With this initial clinical picture of hirsutism, central obesity, polycythemia and lymphopenia, a provisional diagnosis of cortisol and androgen hypersecretion was suspected. Although PCOS is a much more common cause of hirsutism, late development and rapid progression along with metabolic derangements made it less likely. Further testing for Cushing syndrome (CS) revealed an early morning cortisol after 1 mg overnight dexamethasone (low-dose dexamethasone suppression test) of 707 (N:<30 nmol/L). A 24 hours urine collection for free cortisol was 3635 (N: 28–276 nmol/day) and a late night salivary cortisol was also elevated at 67.77 (N: <5.5 nmol/L). The serum adrenocorticotropic hormone (ACTH) was suppressed at 0.7 (N: 2.2–13.3 pmol/L). In addition, the serum androgens, that is, dihydroepiandrosterone-sulfate (DHEA-S), total testosterone and androstenedione were elevated at 16 (N: 0.5–5.6 nmol/L), 7.7 (N: 0.1–1.4 nmol/L) and >34.9 (N: 1.0–11.5 nmol/L), respectively.

These results supported the diagnosis of an ACTH-independent cause of CS. In addition, the cosecretion of cortisol and androgen prompted
Rare disease

<table>
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<th>Table 1 Causes of hirsutism</th>
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<td>Cause</td>
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<tr>
<td>Androgenic hirsutism</td>
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<tr>
<td>Polycystic ovary syndrome (PCOS)</td>
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<td>Non-classical congenital adrenal hyperplasia</td>
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<td>Cushing syndrome</td>
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<td>Androgen-secreting ovarian tumour (eg, Sertoli-Leydig cell tumour)</td>
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<td>Androgen-secreting adrenal tumour (eg, adrenocortical carcinoma)</td>
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<td>Non-androgenic hirsutism</td>
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<td>Drug-induced</td>
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the search for an adrenal tumour with a targeted MRI. A large 10.4×7.7×5.2 cm right adrenal mass abutting the medial liver edge and invading the inferior vena cava was described. These findings were suggestive of an adrenocortical carcinoma (ACC) (figure 1).

TREATMENT

Three weeks after her diagnosis, she underwent debulking surgery with an open right adrenalectomy, inferior vena cava resection and reconstruction and cholecystectomy. The pathology results confirmed high-grade ACC of >10 cm (pT4N0) with a mitotic count of 28/50 per high-power field, Ki67 proliferative index up to 30% with vascular and liver invasion. Figure 2 shows the patient’s histopathological characteristics of her ACC along with immunohistochemistry staining confirming the diagnosis.

OUTCOME AND FOLLOW-UP

Unfortunately, with the late diagnosis and advanced disease, curative surgery was not attained and persistent residual disease was present. She was discharged home postoperatively on hydrocortisone 20 mg daily in the morning. However, given incomplete resection, early morning cortisol levels were assessed more frequently and at the 6-week follow-up visit, the cortisol level was 799 (N: 100–500 nmol/L) before the morning dose.

We believed that this elevated cortisol is indicative of persistent secretion by the tumour rather than recovered left adrenal gland given it is still early for recovery of the contralateral gland and the morning cortisol level never dropped below 490 nmol/L during these 6 weeks after surgery. Based on that, her hydrocortisone was stopped, as well as her amlodipine because her blood pressure normalised.

She is currently undergoing adjuvant chemotherapy with high-dose mitotane, which is an adrenocorticalolytic drug used in patients with ACC. As it will also decrease the normal adrenocortical function, glucocorticoid replacement is routinely given after initiation of mitotane. Monitoring of ACTH and urinary-free cortisol is necessary to adjust glucocorticoids dose. Because mitotane increases cortisol binding globulin levels, serum cortisol is not a useful marker to monitor response to therapy. One of the exceptions to routine initiation of glucocorticoids with mitotane is residual ACC, like in our patient, where monitoring for development of adrenal insufficiency is warranted before starting replacement therapy. Within 1 month of starting mitotane, the ACTH level has risen to 15.8 (N: 2.2–13.3 pmol/L) and the 24 hours urinary-free cortisol dropped to 40 from 236 (N: 28–276 nmol/day). She was then diagnosed with incipient adrenal insufficiency and started on hydrocortisone 10 mg orally two times per day, which was sufficient to decrease the ACTH to 1.2 pmol/L and increase the 24 hours urinary-free cortisol to 221 nmol/day.

DISCUSSION

Hirsutism is mostly caused by excess androgen secretion either from the ovaries or adrenal glands. In premenopausal women, testosterone is produced by the ovaries, while DHEA-S is exclusively from the adrenals. Ovaries and adrenals both contribute...
to the production of DHEA and androstenedione. After meno-
pause, on the other hand, the adrenals become the major source
of androgens in women.

By far the most common cause of hirsutism is PCOS, which
is frequently associated with obesity and anabolic features of
hyperinsulinism (hyperglycemia, hypertension and hyperlipid-
emia). However, when anabolic features (thin skin, purple
striae, myopathy and osteopenia) are present, this should raise
suspicions for hypercortisolism (i.e., CS), a less common but more
serious cause of hirsutism.

The cosecretion of androgens (DHEA-S, testosterone and
androstenedione), which are anabolic steroids, mitigates the
anabolic effects of cortisol excess in the classic CS. The signs
of androgen excess (hirsutism, acne, male-pattern baldness,
preserved muscle bulk and bone mass and erythrocytosis) in our
patient overshadowed the subtle anabolic effects of excess
cortisol (thin skin, bruising, striae and myopathy). This mixed
clinical pattern prompted a search for CS with cosecretion of
cortisol and androgens (a harbinger of adrenal carcinoma).

An important clue to the diagnosis of ACC was the discordant
elevation of DHEA-S coupled with depression of the ACTH
level. Normally ACTH drives secretion of adrenal DHEA-S
and both hormones are elevated in ACTH-dependent Cushing
disease and ectopic ACTH syndrome. However, DHEA-S has a
prolonged half-life in serum (10–16 hours), with relatively stable
levels throughout the day, making it a useful marker for the
detection of chronically suppressed ACTH. Accordingly, ACTH
and DHEA-S are both depressed in benign adrenal adenomas.

ACC is a rare disorder with an incidence rate of ~1–2/
million/year. There is a bimodal age distribution, that is, 1st
and 5th decades of life and women are more often affected than
men—59% versus 41%. On the average, the adrenal tumour
measures 12 cm and weighs 689 g. Unlike adrenal incident-
talomas, 80% of which are non-functional, ~60% of ACC are
functional and secrete excess hormones. Cosecretion of cortisol
and androgens is the most frequent pattern (~45%) and is highly
suggestive of ACC. As with our patient, the anabolic effect of
cosecreted androgens may counteract the glucocorticoids anti-
anabolic effect on skin and muscle, thus masking the clinical
anti-Cushing diagnosis. Unfortunately the mortality rate for advanced
disease remains elevated, that is, 40% and 27.6% in stages III
and IV, respectively.

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Learning points

► Although hirsutism causes are mostly benign, a more
serious aetiology need to be sought if progression is rapid
or accompanying features and metabolic derangements are
present.

► The anabolic effects of cortisol excess (thin skin, easy
bruising, purple striae, proximal myopathy and osteopenia)
attenuate the anabolic effects of hyperinsulinism associated
with obesity and polycystic ovary syndrome and may aid in
the distinction of these two disorders.

► The excess production of androgens mitigates the
anabolic effects of cortisol excess in the classic Cushing
syndrome.

► The cosecretion of cortisol and androgens should raise
suspicion of adrenocortical carcinoma.