CASE REPORT

Florid hyperandrogenism due to a benign adrenocortical adenoma

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Accepted 6 June 2018

SUMMARY

A 26-year-old woman with a history of polycystic ovarian syndrome presented with secondary amenorrhea, worsening hirsutism, acne, deepening of voice and unexplained 10–20 kg weight gain. Her Ferriman-Gallway hirsutism score was 12 with cystic facial acne and increased masculine phenotype. Urine Beta-Human Chorionic Gonadotropins (bHCG) was negative. She had elevated serum testosterone of 551 ng/dL, androstenedione at 7.46 ng/mL and dehydroepiandrosterone sulfate (DHEAS) at 4243 µg/L. Overnight dexamethasone suppression test showed mildly unsuppressed cortisol (2.89 µg/dL). Urinary free cortisol along with paired serum cortisol and adrenocorticotrophic hormone (ACTH) tests were normal (55.4 µg/24 hours, 13.44 mcg/dL, 30.4 pg/mL respectively). Her leutinizing hormone (LH) was low (<0.1 mIU/mL), follicle stimulating hormone (FSH) low/normal (1.41 mIU/mL) with sex hormone binding globulin (SHBG) level 45 nmol/L and the rest of the pituitary and adrenal workup was unremarkable. Thyroid stimulating hormone (TSH) was 2.15 mIU/mL. MRI revealed a 3.1 cm, indeterminate but well-defined left adrenal lesion and polycystic ovaries without abdominal lymphadenopathy. Given radiological appearances and despite biochemical concerns for adrenocortical malignancy, a multidisciplinary team meeting decision was made to proceed with laparoscopic adrenalectomy. Histology was consistent with a benign adenoma. Postoperatively, there was clinical and biochemical resolution of the disease.

CASE PRESENTATION

A 26-year-old woman with a history of PCOS presented with 2 months history of acne and hirsutism, 7 months of secondary amenorrhea, deepening of voice and 9 months of unexplained 10–20 kg weight gain (figure 1). Clinically, she had a Ferriman-Gallway hirsutism score of 12, despite receiving monthly laser therapy, with cystic facial acne and increased masculine phenotype. The patient did not have any central adiposity or striae, moon face, easy bruising, skin thinning or proximal myopathy.

Prior to her presentation, she had experienced regular menses every 30 days since menarche at 12 years old and had been diagnosed with PCOS-spectrum disease by her gynaecologist based on mild hirsutism, polycystic ovarian morphology on transvaginal ultrasound (TVUS) and dysmenorrhea. No labs were done. At around the time of PCOS diagnosis, she did not have any acne or scalp hair loss.

INVESTIGATIONS

Urine pregnancy test was negative. She was found to have male range testosterone level of 551 ng/dL (normal 7–90 ng/dL), elevated androstenedione 7.46 ng/mL (0.29–3.44 ng/mL) and elevated DHEAS 4243 µg/L (normal 450–3200 µg/L), with a follicular phase serum 17-OH progesterone 0.70 ng/mL (normal 0.1–2.3 ng/mL), SHBG 45 nmol/L and normal albumin. Both her LH

BACKGROUND

Oligomenorrhea is most commonly caused by polycystic ovarian syndrome (PCOS). Rapidly progressive, severe hyperandrogenic signs or the presence of virilisation should raise concerns about androgen-secreting tumours even in a patient with a prior diagnosis of PCOS. This is especially true for patients with elevated androgens who present with these features. Extremely high testosterone levels are invariably due to androgen-secreting malignant tumours. However, as evidenced by our case, it is possible for benign lesions to mimic malignant disease both clinically and biochemically. Since such cases are extremely rare and given the challenge of differentiating benign and malignant adrenocortical neoplasms histologically, extra vigilance is required postoperatively with clinical, biochemical (eg, serum androgens with/without urinary steroid profiling) and radiological (CT or MRI adrenals) monitoring.

Figure 1 Acne before adrenalectomy.

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To cite: LaVoie M, Constantinides V, Robin N, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-224804

Figure 2 MRI scan of the adrenals. Well-defined, ovoid left adrenal lesion identified inferiorly at the lateral limb measuring 3.1×2.6×1.8 cm. This was hypointense on T1 with mild signal loss on out of phase images. On T2 images, the lesion had intermediate to slightly high signal with mild internal heterogeneity. Postcontrast images showed prominent enhancement with no major wash out on delayed images. Overall, the adrenal adenoma was characterised as indeterminate.

and FSH were suppressed with values LH <0.1 mIU/mL FSH 1.41 mIU/mL, respectively; estradiol was 32.76 pg/mL (normal 24.5–195). TSH was 2.15 mU/L and prolactin was 404 µIU/mL (102–496 µIU/mL). Her 9 am random cortisol was 13.44 mcg/dL with a coupled ACTH at 30.4 pg/mL (<69 pg/mL), and low dose dexamethasone suppression test revealed cortisol of 2.89 µg/dL (normal <1.8 µg/dL) with a urinary free cortisol level of 55.4 µg/24 hours (normal 36–137 µg/24 hours), where no significant hypercortisolaemia was demonstrated to explain her clinical or biochemical presentation, although slight cortisol cosecretion is possible. Further workup of the adrenal lesion showed normal serum aldosterone and renin and urine fractionated metanephrine levels. To determine the aetiology of her hyperandrogenic state, she underwent TVUS to evaluate for ovarian malignancy in addition to an MRI abdomen/pelvis. TVUS showed appearances of polycystic ovaries and MRI showed an ovoid, well-defined, enhancing 3.1×2.6×1.8 cm left adrenal lesion with some heterogeneity and overall

Figure 3 Pathology specimen. 13 g adrenal gland with well circumscribed 3 cm tumour.

Figure 4 Pathology report. The tumour is composed of sheets of eosinophilic and clear cells (50:50) without any nuclear atypia or necrosis and mitoses <1/10HPF. Ki-67=6% and Weiss score 0.

indeterminate characteristics; other findings included polycystic ovarian morphology with otherwise normal abdominal viscera and no abdominal lymphadenopathy (figure 2). CT thorax with intravenous contrast was negative for lymphadenopathy or evidence of metastasis. Her case was discussed at the Salford NHS Foundation Trust (UK) adrenal MDT who agreed with us that given her clinical, biochemical and radiological characteristics as well as the fact that she had no insurance cover for the investigations per se, there was sufficient evidence to proceed with adrenalectomy without having to be subjected to further imaging investigations.

DIFFERENTIAL DIAGNOSIS

We want to understand how the final diagnosis is teased out. This is often the most important section and needs to be substantially discussed. All working diagnoses need to be substantiated.

TREATMENT

Given the uncertainty involved, the patient was also discussed in the adrenal multidisciplinary team meeting at Imperial College NHS Trust (Hammersmith Hospital, London, UK). The decision was made to proceed laparoscopically with intraoperative assessment of locoregional tumour extension. During the operation, the tumour was found to be completely enveloped by healthy capsule/fascia with no evidence of local invasion (figure 3). The operation was completed laparoscopically with perioperative glucocorticoid coverage, respecting oncological principles and achieving a R0 resection. Histology was consistent with benign adenoma with Ki67=6% and a Weiss score of 0 (diagnosed both locally in ECC Labs-IHCS Histopathology centre, Nicosia, Cyprus as well as Massachusetts General Hospital, Massachusetts, USA) (figure 4). One month after the adrenalectomy, the patient restarted with normal menstrual cycles in addition to losing 11 kg in weight (while also dieting). Repeat labs showed normal levels of testosterone (21.8 ng/dL), androstenedione (1.19 ng/mL), DHEAS (1420 ng/mL) and LH (6.85 mIU/mL) (table 1).

Table 1 Labs before and after surgery			
	Reference range	Preop	Postop
Testosterone	7–90 ng/dL	551 ng/dL	21.8 ng/dL
Androstenedione	0.29–3.44 ng/mL	7.46 ng/mL	1.19 ng/mL
DHEAS	450–3200 µg/L	4243 µg/L	1420 ng/mL
17-OH progesterone	0.1–2.3 ng/mL	0.70 ng/mL	
Unfractionated urine cortisol	Normal 36–137 µg/24 hours	55.4 µg/24 hours	
Overnight dexamethasone suppression test	<1.8 µg/L	13.44 µg/L	
DHEAS, dehydroepiandrosterone sulfate.

Figure 5 Almost complete resolution of acne 1 month after adrenalectomy.

OUTCOME AND FOLLOW-UP

At 6-month and 12-month evaluations, she was in full remission both clinically (normal menstrual cycles, no acne and minimal to no hirsutism) and biochemically (with normal levels of androgens and other labs) (figure 5). CT scan of the abdomen at approximately 6 months was clear of any malignant or metastatic disease and she is now awaiting MRI scan of the abdomen (to try and reduce radiation exposure) and was also offered urinary steroid profiling which she is considering.

DISCUSSION

Hyperandrogenic states in females can present with virilisation and reproductive dysfunction. In patients who have rapid onset of the aforementioned symptoms, a further workup should be done to exclude the presence of ovarian or adrenal neoplasia. If testosterone is greater than 200 ng/dL, it is more likely due to a pathological aetiology and further workup should be obtained.^{1,2} A LDDST can be helpful since there is evidence that a 40% or greater decrease of serum testosterone following LDDST can help to distinguish virilising tumours from other causes of hyperandrogenism³; notwithstanding, there is no absolute cut-off to distinguish all the cases of these two entities and further replication and validation of this diagnostic test is warranted (Professor Gregory Kaltsas, personal

communication). Further workup includes imaging of the ovaries and adrenal glands.⁴ While the most common aetiology of a hyperandrogenic state is ovarian, adrenal pathology must also be considered, especially if DHEAS or androstenedione are elevated. Compared with other studies, our patient was found to have a severely elevated testosterone level in addition to elevated androstenedione and DHEAS (table 2).

Since our patient had an elevated DHEAS, unlike ACTH-independent (subclinical) hypercortisolism where DHEAS is typically decreased due to the chronic suppression of ACTH, she did not have significant hypercortisolism.⁵ Given the hyperandrogenism combined with her mildly unsuppressed cortisol levels and an adrenal lesion the concern that this was an adrenocortical carcinoma was raised. However, the final histology indicated that this was a benign lesion as confirmed by two histopathological centres who independently examined the tumour. This diagnosis is also supported by her subsequent clinical, laboratory and radiological course over a follow-up period of almost 2 years. Therefore, this case illustrates that even adrenal adenomas can cause very high androgen levels and hence the androgen levels per se cannot fully discriminate between adrenal adenomas and carcinomas. Notwithstanding, given the inherent difficulties with differentiating adenomas and carcinomas histopathologically⁶ and following advice

Table 2 Androgen level comparison

Article author	Testosterone (ng/dL)	DHEAS (µg/L)	Androstenedione (nmol/L)	17-ketosteroid (mg/day)
Index case	551	4243	7.46	NA
Sakuma ⁹	250	2752	6.73	203.4
Micić ¹⁵ (bilateral adenoma)	414	5158	10.7	3.6
Kamenicky ¹⁶	NA	1197*	NA	NA
Mattox ²	510	30500	NA	<0.01
Derksen ¹⁷ (two adenoma cases)	NA† 17‡	5490† 10130‡	9.62† 1.88‡	47† 50‡
Yang ¹⁸	96.54	4640	NA	NA
Tong ¹⁰ (eight patients w/adenomas)	118–1154	2100	NA	NA
Dolinar ¹¹	650	2100	NA	7.2
Murakami ¹²	507	4237	NA	NA
Werk ¹³	NA	NA	NA	9.5–20.2
Schteingart ¹⁴	320	2400	0.37	17.5

Key: Reference values: Testosterone (Female)=7–90 ng/dL; DHEAS=450–3200 µg/L; Androstenedione=0.29–3.44 ng/mL; 17-ketosteroid (Female)=5–15 mg/24 hours.

Conversions

*Highest value in the study.

†Patient 1 in Derksen study.

‡Patient 2 in Derksen study.

Androstenedione, nmol/L x 0.349=ng/mL; DHEAS, ng/mL x 0.00271 = µmol/L; Testosterone, ng/mL x 3.47=nmol/L.

DHEAS, dehydroepiandrosterone sulfate; NA, not available.

from a reference centre on adrenal disease (Professor Wiebke Arlt, Birmingham, UK, personal communication), we have implemented and propose close monitoring in all such cases with clinical, biochemical (serum androgens coupled with urinary steroid profiling if available) and radiological surveillance.^{7,8} In particular, we would advocate clinical, biochemical and cross-sectional imaging surveillance every 6 months. Unfortunately, our patient declined testing at intervals every 6 months and instead is willing to do annual checks.

Throughout the literature, patients with androgen-producing adrenal adenomas all had resolution of virilisation, hirsutism and biochemical markers after successful surgery. There is variable follow-up among the studies, but for the most part it appears there is little to no risk of recurrence or malignant transformation within the first year after surgery.^{4,9–14} Tong *et al* described a patient with a Weiss score of 4 and Ki-67 of 3% who had local recurrence as noted by elevated testosterone and DHEAS levels 5 years after her initial surgery, whose symptoms and abnormal biochemistry again resolved after repeat surgery.⁴ Again, such cases illustrate the need for close postoperative surveillance of such patients.

Despite the patient having polycystic ovaries, it additionally became evident that this was not the cause of her hyperandrogenic state. This is a secondary take-home message from this case as very high serum androgens or a rapid onset of symptoms should raise suspicion of an ovarian or adrenal lesion as being the cause, especially considering that polycystic ovarian morphology with/without overt PCOS is common and thus dual pathology should also be considered.

Learning points

- ▶ Rapidly progressive or severe hyperandrogenic signs or the presence of virilisation should raise concerns about androgen-secreting tumours.
- ▶ While the most common cause of a significant hyperandrogenic state is related to ovarian pathology, in patients with extremely elevated testosterone >200 ng/dL, especially if dehydroepiandrosterone sulfate is elevated, a thorough evaluation of the adrenal glands should be undertaken.
- ▶ In cases of florid hyperandrogenism due to androgen secreting benign adenomas, we recommend long-term and regular clinical, biochemical and radiological surveillance since the natural history of these lesions is unknown and because there have been instances of malignant transformation.

Acknowledgements Special thanks to Dr Basil Issa, endocrinologist from South Manchester University Hospital and Dr Safween Adan, endocrinologist from Central Manchester Foundation Trust.

Contributors MLV: resident on case. Wrote majority of case. AK: main attending, decided patient care along with necessary imaging and labs. Supplied writer with information regarding the patient history, labs, imaging and management. Major editor. VK: surgeon involved who provided pictures and pathology. NR: Edited our drafts.

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 Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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