

Case report

A unique case of a benign adrenocortical tumor with triple secretion of cortisol, androgens, and aldosterone. Development of multiple sclerosis after surgical removal of the tumor

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ABSTRACT

We present a 39-year old female with a benign adrenal tumor characterized by autonomous secretion of cortisol, androgens, and aldosterone. The patient presented with a 4-year history of hypertension and severe hirsutism. Baseline investigations revealed elevated testosterone, androstendione, and 17OH progesterone with normal levels of dehydroepi androsterone sulfate. CT of the adrenals revealed a 2.5x3.0 cm tumor with characteristics of an adenoma on the left adrenal gland. Pelvic ultrasound was normal. Further investigations revealed suppressed basal ACTH levels, loss of diurnal rhythm of cortisol, and failure to suppress on low dose dexamethasone suppression test, suggesting autonomous cortisol secretion by the tumor. She had an exaggerated response of 17OH progesterone to ACTH, implying reduced 21-hydroxylase activity. An elevated plasma aldosterone concentration to plasma renin activity ratio was suggestive of hyperaldosteronism, which was confirmed by failure of aldosterone to suppress to a formal saline infusion test. Complete clinical and biochemical remission of the disease was observed after left adrenalectomy. Histology confirmed the presence of an adrenocortical adenoma. The patient developed multiple sclerosis 6 months after the operation. The flare-up of an autoimmune disease (multiple sclerosis) postoperatively could be coincidental or possibly related to the high normalization of the high cortisol levels acting as a precipitating factor.

Key words: Adrenocortical adenoma, Multiple sclerosis, Cushing's syndrome, Hyperaldosteronism

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INTRODUCTION

Hirsutism is the most evident and most disturbing clinical feature of androgen excess in women of reproductive age and is usually of ovarian origin. Polycystic ovary syndrome (PCOS) is the commonest cause of hyperandrogenaemia, with other identifiable causes being classic and non-classic congenital adrenal hyperplasia (CAH), hyperandrogenic insulin resistance, usually associated with acanthosis nigricans syndrome, and androgen-secreting neoplasms.¹ Cortisol and aldosterone are the hormones most frequently secreted by adrenocortical tumors, whereas isolated androgen secretion by such tumors is extremely rare.² Mixed cortisol and androgen secretion by adrenal adenomas have also been reported,³⁻⁵ although such a syndrome combining virilization and Cushingoid appearance is more common in adrenal carcinomas. Mixed cortisol and aldosterone secretion by adrenal adenomas have also been described.^{6,7} However, a benign adrenal tumor simultaneously secreting cortisol, aldosterone, and testosterone has not to our knowledge been previously reported. This rare occurrence is herein described.

CASE REPORT

A 39-year old female was presented to our department with a 4-year history of fatigue, severe hirsutism, acne, and symptoms of depression for which she had been treated with lithium. She had also been found to be hypertensive (170/90 mmHg). Her menstrual cycles were regular.

On examination, her blood pressure was found to be well controlled on propranolol 25mg and felodipine 5mg daily (120/80 mmHg). She had facial hair growth with a Ferriman-Gallwey score of 20, facial acne, and oily skin, and her body mass index (BMI) was 24. The rest of the examination was unremarkable and no Cushingoid features were present.

After a washout period of her antihypertensive treatment, baseline investigations revealed significantly elevated testosterone levels at 2.8 ng/ml (NV: 0.1-0.9ng/ml), androstendione (Δ_4A) at 9.4 ng/ml (NV: 0.5-2.8 ng/ml), and 17OH progesterone (17OHP) at 14.7 ng/ml (NV: 0.1-1.0ng/ml). DHEAS was well within the normal range at 2212 ng/ml (NV: 350-4300ng/ml). Plasma renin activity (PRA) was

2.2 ng/ml/hr (NV: 1.5-5.7ng/ml/hr) with elevated plasma aldosterone concentrations (PAC) of 966 pmol/L (N.R: 97-831 pmol/L). A 09.00 cortisol level was 454 nmol/L (NV: 138-690 nmol/L) with suppressed ACTH (<5 pg/ml, NV: 9-52 pg/ml). Thyroid function was normal. Serum K⁺ was 4.0 mmol/L and Na was 145 mmol/L.

The hyperandrogenaemia with marked elevation of 17OHP raised the suspicion of an adrenal cause. CT of the adrenals revealed a left adrenal mass of 3.0X2.5 cm with characteristics of an adenoma (homogeneous, well-defined lesion with clear margins that did not show enhancement after the administration of iv contrast material).

We therefore proceeded to further investigate the functional status of the adrenal mass. Repeated PAC was 285pmol/l (10.27ng/dl) with a PRA of 0.4 ng/ml/hr, giving a PAC (ng/dl) to PRA ratio of 25.68, suggestive of autonomous aldosterone secretion. After infusion of two liters of normal saline within four hours, PRA was suppressed to 0.2 ng/ml/hr and PAC was reduced to 118 pmol/l, a value which in the presence of undetectable ACTH levels is considered inadequately suppressed according to our laboratory reference range (<50 pmol/l). Potassium levels were within normal range. A short synacthen test (SST) revealed an exaggerated response of 17OH progesterone and aldosterone (Table 1). Diurnal rhythm of cortisol was lost (360nmol/l and

Table 1. SST: 17OH progesterone, cortisol, and aldosterone response to 250 µg of synacthen given IV.

| Time (min) | 17OH progesterone (ng/ml) | Cortisol (nmol/l) | Aldosterone (pmol/l) |
|------------|---------------------------|-------------------|----------------------|
| 0 | 16.3 | 495 | 1520 |
| 30 | >25 | 699 | 1729 |
| 60 | >25 | 693 | 1749 |

Expected levels of 17OHP after stimulation: <9.7 ng/ml

Table 2. LDDST: 0.5mg of dexamethasone 6-hourly for two days (expected cortisol levels <25 nmol/L).

| | Day 1 (08.00) | Day 3 (08.00) |
|-------------------|---------------|---------------|
| CORTISOL (nmol/L) | 394 | 538 |
| ACTH (pg/ml) | <5 | <5 |

500nmol/l at 08.00 and 24.00, respectively), while a low dose dexamethasone suppression test (LDDST) showed autonomous cortisol secretion (Table 2), which was in keeping with the suppressed basal ACTH levels. The catecholamines, nor-metanephrines, and VMA concentrations in a 24hr urine sample were within normal range, excluding the diagnosis of a pheochromocytoma. An oral glucose tolerance test (OGTT) with 75gr of glucose revealed a degree of insulin resistance. Further imaging with ultrasonography showed normal ovarian morphology and normal uterus.

The diagnosis of a cortisol, androgen, and aldosterone secreting adrenal adenoma was therefore made. The patient underwent left laparoscopic adrenalectomy. Postoperatively she had an uneventful recovery with no need for anti-hypertensive treatment. Repeated hormonal evaluation revealed normalization of her androgen levels: testosterone 0.2ng/ml, androstendione 0.4ng/ml, 17OHP 0.8ng/ml and DHEAS 226 ng/ml. PAC and active renin (AR) were within normal range at 158pmol/l and 13.4 MU/ML (NV: 7-76MU/ML, respectively). A SST showed a marginal peak cortisol level at 506 nmol/l (>580nmol/l) and a peak 17OHP level at 3.8ng/ml, which was normal. She had a normal diurnal rhythm of cortisol (335 and 32 nmol/l at 08.00 and 24.00, respectively), and she suppressed cortisol at 20nmol/l after a LDDST. After completion of the LDDST, we performed an infusion of two liters of normal saline within 4 hours and the level of PAC was found to be suppressed <50pmol/l, indicating complete cure after the tumor removal. Histology confirmed the presence of an adrenocortical adenoma with no evidence of capsular or vascular invasion.

The patient was discharged on hydrocortisone tablets to be taken during stress. Reassessment of the patient two months later showed normal adrenal function. During a follow-up period of 8 months she had complete remission of her hirsutism. A Bone Mineral Density (BMD) scan of the spine revealed osteoporosis for which she was treated with bisphosphonates. Six months postoperatively she presented to the Neurology Department with a 6-day history of gradual onset of numbness, decreased sensation and paresis of the left lower limb, and weak-

ness of the left upper limb. On examination, she had impaired sensation of the left lower limb with abnormal plantar reflexes. Examination of the CSF was normal. Subsequent MRI of the brain showed lesions compatible with demyelinating disease of the right frontal and parietal lobe. She was treated with intravenous steroids for 5 days followed by clinical improvement.

DISCUSSION

We present a very rare case of a patient with a benign adrenocortical tumor and autonomous secretion of cortisol, androgens, and aldosterone. Following surgical removal of the tumor, the patient presented a clinical picture of multiple sclerosis (MS). A triple hormonal secretion (cortisol, aldosterone, and androgens) by a benign adrenocortical tumor has not previously been described.

Despite the absence of full-blown clinical Cushing's syndrome, the autonomous secretion of cortisol by the tumor was demonstrated by the loss of diurnal rhythm of cortisol, the absence of cortisol suppression on the LDDST,⁸ and the concurrent suppressed basal ACTH levels.

In adrenal incidentalomas, defects in the enzymatic activity of enzymes involved in steroidogenesis, such as 21-hydroxylase, 11 β -hydroxylase, 17 α -hydroxylase, and 17,20-lyase, have been described that could represent either functional impairment of the enzyme activities or gene mutations restricted to the tumor.⁹⁻¹³ In our case reduced activity of 21-hydroxylase within the tumor (normal 17OHP levels after tumor excision) could account for the exaggerated response of 17OHP to ACTH, and the increased testosterone, and Δ_{4A} levels. Similar over-response of 17OHP to ACTH has been described before in ten patients with sub-clinical Cushing's syndrome,¹⁴ showing that alterations in enzymatic pathways can coexist with the presence of cortisol autonomy. Co-secretion of cortisol and androgens (elevated DHEAS, Δ_{4A} , and testosterone) has also been described in six cases of adrenal tumors where there was no evidence of malignancy.³⁻⁵ In these cases the association between hypercortisolism and hyperandrogenaemia could be explained by increased 17,20-lyase activity secondary to increased cyto-

chrome b5 expression in the adrenal adenoma tissues, as described by Sakai et al.⁵ Combined cortisol and aldosterone secretion from adrenocortical adenomas has also been described.^{6,7} The DHEAS values, although normal prior to surgery, decreased considerably, post-operatively, possibly indicating that DHEAS was also secreted by the adenoma.

In our case there was autonomous secretion of aldosterone because of the inadequate suppression of aldosterone levels after salt loading. To date, the PAC/PRA ratio is the most widely used screening test for distinguishing patients with essential hypertension from those with possible primary aldosteronism.¹⁵ If this ratio is higher than 20, primary hyperaldosteronism is suspected and further confirmation should be provided with salt loading and measurements of aldosterone levels.^{16,17} The cut-off value of aldosterone, at the end of the saline infusion that has been used in order to confirm or exclude hyperaldosteronism, varies according to different authors between 138 pmol/l (5ng/dl) and 270 pmol/l (10 ng/dl).^{18,19} It is quite possible that such a wide range exists because other renin independent factors influence aldosterone secretion. Among these factors ACTH is considered to be the most important one, as it has been shown to have an acute stimulatory effect on aldosterone in both normal subjects and in patients with functional adrenocortical tumors.^{20,21} However, its role on the interpretation of aldosterone secretion tests has not been validated to date. We therefore consider that if ACTH is suppressed (as in our case), thus eliminating its effect on aldosterone secretion, the cut-off value for aldosterone suppression after salt loading should be even lower than the currently used values. In fact, in our series of 40 subjects (with or without essential hypertension and normal CT of the adrenals), in whom we performed saline infusion (2lt of normal saline over a 4hour period) after an overnight dexamethasone suppression test (1mg dexamethasone), we have shown the cut-off value of PAC to be 50 pmol/l (unpublished data). The normal K⁺ levels in our patient are not incompatible with autonomous aldosterone secretion by the tumor, since normokalaemic primary aldosteronism constitutes a common presentation of the disease.^{18,22,23} Therefore, using these criteria we consider that our pa-

tient had autonomous secretion of aldosterone in addition to cortisol and androgens. Normalization of her hormonal profile and blood pressure and remission of her hirsutism following surgery support our diagnosis.

Multiple sclerosis is a chronic demyelinating disease of the central nervous system (CNS), most probably of autoimmune pathogenesis. Both T-cell and B-cell activation with antibody formation have been shown to be implicated.²⁴⁻²⁷ Glucocorticoids exert their immunosuppressive effects through inhibition of immunoglobulin synthesis, stimulation of lymphocyte apoptosis, and inhibition of cytokine production. It is therefore possible that after the immunosuppressive effects of hypercortisolism were removed following tumor excision, our patient developed an autoimmune disease. The abrupt elimination of hypercortisolism following tumor excision possibly acted as a precipitating factor. A cortisol deprivation syndrome after cessation of supraphysiological glucocorticoid levels has been well described and favors this assumption.²⁸

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