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Dexamethasone-suppressible feminizing adrenal adenoma

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Summary: A 39 year old man presented with gynaecomastia, loss of libido and high blood pressure. Hormone studies revealed elevated plasma levels of oestradiol and its precursors, which increased in response to adrenocorticotrophic hormone and were reduced to normal levels with dexamethasone. Computed tomography disclosed a left adrenal mass and surgery was performed. The removed tumour weighed 84 g and the histological diagnosis was of adenoma. Nine years after surgery, he is asymptomatic, without hypertension, and radiological and or hormonal evidence of recurrence. We discuss the hormone profile in this case and the dynamics of steroid production by the tumour which, in contrast to the classical concept of tumour autonomy, showed dependence of oestradiol secretion on endogenous adrenocortico- trophic hormone.

Introduction

Feminizing tumours of the adrenal cortex are rare and usually malignant neoplasms.[1] They are almost exclusively confined to middle-aged men and produce symptoms that reflect the oestrogen excess and androgen deficiency – gynaecomastia, diminished libido and testicular atrophy.[2] As in other adrenal tumours, there is no close relationship between the histopathology and the biological behaviour of the neoplasm.[3]

We present a patient with a feminizing adrenocortical adenoma after a post-resection follow-up period of over 9 years. Hormone production by the tumour was unexpectedly suppressible with dexamethasone. We present its hormone pattern and discuss the different parameters used to differentiate the biological behaviour of adrenocortical tumours.

Case report

A 39 year old man was evaluated for a 5 year history of progressive bilateral gynaecomastia and diminished libido without impotence. His right testicle was cryptorchid at birth and had never descended into the scrotum. Physical examination revealed no features of Cushing's syndrome. Blood pressure was 180/120 mmHg. Breasts were Tanner's stage IV, without tenderness or galactorrhea; no palpable abdominal masses were felt and sexual hair had a feminine distribution with absence of thoracic hair. The right testicle was not palpable and the left had a soft consistency and a volume of 20 cm.[3]

Blood count, urinalysis and blood biochemistry, as determined in the SMA-12 autoanalyser, and plain X-rays of the chest, abdomen and skull were normal. Serum levels of β-human chronic gonadotrophin, α-fetoprotein and carcinoembryonic antigen were undetectable. Urinary vanilly mandelic acid and total metanephrine excretion were normal, as was urinary excretion of free cortisol. Other hormone studies are shown in Table I. Baseline serum levels of oestradiol (E2), progesterone (P) and 17-hydroxyprogesterone (17OH-P) were elevated but plasma testosterone levels were normal, as was urinary excretion of 17-ketosteroids (17KS). Intravenous infusion of β_{1-24} corticotrophin (ACTH; 0.25 mg) for 8 hours produced substantial increases in the levels of E2, P, 17OH-P and 17KS with no change in testosterone. Dexamethasone 0.5 mg/6 hours for 2 days decreased the levels of E2, P and 17OH-P to normal values and suppressed the plasma cortisol value to below 140 nmol/l. Intramuscular injection of human chorionic gonadotrophin (hCG) (5,000 IU daily for 3 days), performed 2 weeks after dexamethasone administration, did not change any hormonal values. Plasma luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels were low to normal, with response to luteinizing hormone releasing hormone (LHRH) (100 µg IV, bolus) (Table II). The plasma aldosterone level was 0.92 nmol/l (normal upright value: 0.11 – 0.84) and upright plasma renin activity while on a low sodium diet was 2.35 ng/l/second (normal value: 1.1 – 2.25), both slightly increased. Chromosomal karyotype was 46XY. Computed tomography (CT) of the abdomen revealed a homogeneous mass in the left adrenal gland measuring 5 – 6 cm in diameter (Figure 1). The right testicle was not

Table I Hormone studies performed prior to surgery

Medication	Time	Oestradiol (pmol/l)	Progesterone (nmol/l)	Testosterone (nmol/l)	Cortisol (nmol/l)	17OH-P (nmol/l)	17-KS (µmol/day)
None	8 hours	1,193	5.5	26.0	356	34	40
ACTH	8 hours	1,267	7.3	23.6	552	69	43
	16 hours	2,037	>127	25.0	1,062	314	194
Dexamethasone	Day 2	371	1.0	21.5	–	–	–
	Day 3	220	0.9	26.7	80	4	33
HCG	Post	496	3.5	33.6	232	34	43
Normal basal values		<220	<3.2	10–35	220–660	1.5–7.5	31.5–77

Table II Luteinizing hormone (LH) and follicle stimulating hormone (FSH) before and after surgery. Values are expressed in IU/l

	LH*	LH†	FSH*	FSH†
Before surgery	5.5	29.3	3.9	7.7
Immediate post-operative period	13.9	–	13.6	–
Three months after surgery	3.5	43.5	4.8	17.1

*Basal value; †peak value after LHRH (100 µg i.v.).

Figure 2 Histological section of the feminizing adrenal neoplasm showing cells with abundant finely granular cytoplasm, similar to those of the zona fasciculata of the adrenal cortex, without mitoses or vascular invasion (H&E, original magnification, × 400).

Figure 1 Abdominal CT scan showing the presence of a homogeneous isointense mass in the external branch of the left adrenal gland, corresponding to the adenoma (indicated by a white square in its interior).
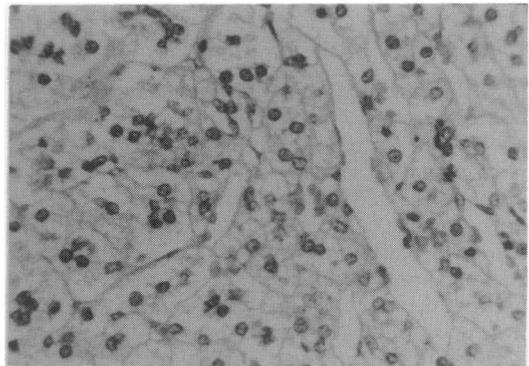
observed either in CT or abdominal ultrasonography. The ^{99}Tc bone scan and hepatic scintigraphy were normal. In the ejaculate, 5.7 ml of seminal fluid were collected, with 8.4 million sperm/ml, 20% of which had spontaneous motility.

The patient underwent laparotomy, with removal of an encapsulated left adrenal mass and the surrounding left adrenal gland. No glucocorticoid replacement was required during or after surgery. The tumour, oval-shaped, was well encapsulated, measured 5 × 4 × 4.5 cm and weighed 84 g. Histologically, it was composed of cells with finely granular cytoplasm, similar to those found in the zona fasciculata of the adrenal cortex. Mitoses were not present and there was no evidence of capsular or vascular invasion (Figure 2).

Postoperatively, the basal levels of all measured steroids as well as the responses to ACTH and dexamethasone were within normal range (Table III). Three months after surgery, the CT was normal and the aldosterone and renin levels had become normal. The values of FSH and LH showed a greater response to LHRH (Table II). In subsequent check-ups, his libido and body hair increased progressively. The gynaecomastia decreased partially in the first 3 months, subsequently requiring bilateral mammoplasty. Four months after surgery, the ejaculate sperm count was 20.2 million/ml, 70% with spontaneous motility. Nine years later, the patient is asymptomatic, normotensive with normal hormone levels.

Table III Hormone studies performed 2 weeks and 3 months after surgery. For reference values see Table I

Medication	Time	Oestradiol (pmol/l)	Progesterone (nmol/l)	Testosterone (nmol/l)	Cortisol (nmol/l)	170H-P (nmol/l)	17-KS (μmol/day)
None*	8 hours	37	1.1	30.2	356	7.8	–
None†	8 hours	95	1.1	29.4	353	3.9	51
ACTH†	8 hours	169	0.8	21.2	229	3.9	–
	16 hours	140	7.9	17.7	527	7.9	54
Dexamethasone	Day 2	121	1.1	14.6	<27	–	–
	Day 3	125	0.9	20.4	<27	1.2	50

[a]*Studies 2 weeks after surgery; [b]†studies 3 months after surgery.

Discussion

Most feminizing adrenal tumours occur in males between 25 and 45 years of age, although some have also been reported in females,[4,5] and before puberty in both sexes.[6-10] Since Gabrilove's review in 1965,[1] updated 5 years later by the same author,[11] only isolated cases have been reported. In this review, 61 cases were studied, six of which were adenomas and the remainder carcinomas. As in our patient, the most common presenting complaint was gynaecomastia accompanied by varying degrees of hypogonadism. Testicular dysfunction is probably due to the inhibitory effect of the oestrogen excess on the secretion of gonadotrophins. It appears that endogenous hyperoestrogenism suppresses the secretion of biologically active LH as compared with immunologically active LH.[2] This would explain a certain degree of response of LH to LHRH, as in the case presented, in which this response increased after removal of the tumour. Moreover, the sustained oestrogen excess could impair testicular steroidogenesis by inhibiting the enzymes dependent on the cytochrome $P450_{c17}$.[2,12]. This latter mechanism would explain the absence of responses of testosterone to hCG in our patient, despite it being testosterone of testicular origin; as shown by its lack of increase after the infusion of ACTH. At the same time, the increase in the hepatic synthesis of sex hormone-binding globulin induced by hyperoestrogenism would explain the total testosterone determinations being within the normal range.

Hypertension is occasionally present in feminizing adrenal tumours,[1] and is usually secondary to the tumour secretion of mineralocorticoids, mainly desoxycorticosterone[13] and sometimes aldosterone.[14] In our case, the non-suppressed renin value excludes the possibility of an autonomous production of mineralocorticoids. We believe that the arterial hypertension, which disappeared following excision of the tumour, could be a consequence of the oestrogen excess. These hormones increase the hepatic synthesis of renin substrate, which leads to an increase in plasma angiotensin II and aldosterone[15] levels.

Some authors have suggested excessive extra-glandular aromatization of precursors to explain the increased oestrogen levels in these tumours.[8,16,17] The return of oestradiol to normal levels and the disappearance of its increase in response to ACTH after surgery is in agreement with tumour production in our case.

Adrenal tumours may be relatively or absolutely deficient in one or more enzymes involved in normal steroidogenesis, such as 21-hydroxylase, 11β-hydroxylase or 3β-hydroxysteroid dehydrogenase.[18] The lack of cortisol hypersecretion or an autonomous production of mineralocorticoids, in spite of the increased availability of precursors in our patient, suggests a 21-hydroxylase deficit.

The secretion of oestrogens and their precursors in response to ACTH has been reported previously in feminizing adrenal tumours *in vivo*[19] and *in vitro*.[20] Similarly, about half of adrenal adenomas producing Cushing's syndrome[21] respond to exogenous ACTH with an increase in 17-hydroxy-corticosteroids. Saez *et al*.[22] demonstrated the existence of binding sites for the ACTH molecule on adrenal tumour membranes.

In spite of their capacity to respond to exogenous ACTH, most tumours derived from steroidogenic tissue function independently of trophic hormone control. The patient reported here is unusual because the administration of dexamethasone reduced oestradiol and its previously elevated precursors to normal levels. This suggests that the tumour hormone production was at least partially dependent on pituitary ACTH.

In the literature reviewed, there is only one report of an oestrogen-producing adrenal tumour whose levels were partially reduced with dexamethasone.[5] These authors suggested that the aromatase activity of the tumour was either dependent on ACTH or directly inhibited by dexamethasone, as in other tissues under experimental conditions.[23] This latter mechanism cannot be applied in our case because dexamethasone

reduced not only oestradiol, but progesterone and hydroxy-progesterone as well, which is not explained by changes in the aromatase activity alone. Perhaps some cases of adrenocortical feminizing syndrome, initially described as non-tumoural,[24] were adenomas susceptible to suppression by dexamethasone and invisible to the radiological techniques available at the time.

Differentiation between benign and malignant tumours of the adrenal glands still remains the main problem and only the existence of metastases is a reliable indicator of malignancy. The regular density of CT (with no necrosis or calcification),[25] a tumour weight of less than 30 g,[26] the absence of mitoses, cellular pleomorphism and vascular or capsular invasion on microscopic examination,[27] as well as urinary 17 ketosteroid levels below 20 mg/day[21,28] and, in some series, the response to ACTH,[21] are characteristic of benign tumours. Our patient demonstrated all these features with the exception of the tumour weight (84 g). However,

the long follow-up period without recurrence supports the benign nature in this case. Finally, the application of modern chromatographic techniques in the analysis of the urinary steroid profile,[29,30] flow cytometry analysis of the tumour tissue[16] and the study of the steroid profile of the aldosterone synthesis pathway[31] provide new approaches for the differential diagnosis.

In summary, we present a further case of feminizing adrenal adenoma where hormone synthesis depended, at least in part, on the endogenous ACTH. This is exceptional and illustrates a failure in the dexamethasone suppression test to determine the tumoural nature of an oestrogen excess of adrenal origin.

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