CASE REPORT

Prolonged remission after long-term treatment with steroidogenesis inhibitors in Cushing's syndrome caused by ectopic ACTH secretion

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Abstract

Spontaneous remission is rare in ectopic ACTH syndrome (EAS). We describe four patients with presumed EAS in whom long-term treatment with steroidogenesis inhibitors was followed by prolonged remission of hypercortisolemia. Biochemical testing was consistent with EAS, but imaging failed to identify a tumor. Patients were treated with ketoconazole alone or with mitotane and/or metyrapone to control hypercortisolemia. Dexamethasone was added when a block and replace strategy was used. Treatment with steroidogenesis inhibitors for 3–10 years in these patients was followed by a prolonged period of remission (15–60 months). During remission, the first patient had an elevated ACTH, low cortisol and 24-h urinary free cortisol (UFC), and adrenal atrophy on computerized tomography scan during remission, suggesting a direct toxic effect on the adrenal glands. Cases 2 and 3 had normal to low ACTH levels and low-normal UFC, consistent with an effect at the level of the ectopic tumor. They did not have a history of cyclicity and case 3 has been in remission for ~5 years, making cyclic Cushing's syndrome less likely. Case 4, with a history of cyclic hypercortisolism, had normal to slightly elevated ACTH levels and low-normal UFC during remission. The most likely etiology of remission is cyclic production of ACTH by the ectopic tumor. Spontaneous and sustained remission of hypercortisolemia is possible in EAS after long-term treatment with steroidogenesis inhibitors; a drug holiday may be warranted during chronic therapy to evaluate this. The pathophysiology remains unclear but may involve several different mechanisms.

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Introduction

Spontaneous remission in Cushing's syndrome is rare; most cases probably represent infarction of an ACTH-secreting pituitary adenoma (1, 2, 3, 4). Transient resolution of hypercortisolism, with inter-cyclic periods as long as 4 years, is most common in Cushing's disease (5, 6). Few cases of sustained spontaneous remission have been documented in ectopic ACTH syndrome (EAS) (7, 8). In this article, we describe four cases of presumed EAS where a prolonged remission followed long-term treatment with steroidogenesis inhibitors. Our aim is to make readers aware of this possibility and urge them to assess intermittently for remission in patients receiving chronic treatment with these agents.

Methods

All patients had confirmation of Cushing's syndrome and evaluation of its etiology at the initial National Institutes of Health (NIH) visit after discontinuing any

steroidogenesis inhibitors for 6 weeks or more. Biochemical testing including corticotropin-releasing hormone (CRH) stimulation test, 8 mg dexamethasone suppression test (DST), and inferior petrosal sinus sampling (IPSS) was consistent with EAS. As previously reported, imaging studies (computerized tomography (CT) and magnetic resonance imaging (MRI) of neck, chest, abdomen, pelvis, and standard 6 mCi dose octreotide scan) performed every 6–12 months failed to identify a source (9) (cases 31–34). Some patients received [¹⁸F]L-3,4-dihydroxyphenylalanine positron emission tomography scans, 64-slice gated cardiac CT, cardiac MRI, or an 18 mCi dose octreotide scan (9).

Case 1

A 42-year-old man presented in 1999 with weight gain, moon facies, proximal muscle weakness, easy bruising, violaceous striae, and an elevated 24-h urinary free cortisol (UFC) and ACTH. IPSS suggested an ectopic source of ACTH. Perhaps because of a 5 mm pituitary

mass seen on MRI, the patient underwent hemihypophysectomy at the outside institution, but hypercortisolemia persisted and no tumor was seen on pathology. Another institution's evaluation was consistent with EAS; ketoconazole was initiated when no tumor was found.

At the NIH in 2003, biochemical testing was consistent with EAS and imaging did not identify a source of ectopic ACTH (Table 1). Eucortisolism was achieved initially with ketoconazole, but subsequently he required metyrapone (in 2004) and mitotane (in 2008) to maintain eucortisolism (Fig. 1A). After ketoconazole was discontinued because of liver enzyme elevations, UFC, though improved, remained elevated (100–268 µg/day and 298.1–739.7 nmol/day), and bilateral adrenalectomy was considered.

In June 2009, the patient developed clinical acute adrenal insufficiency; cortisol was 4 µg/dl (110.4 nmol/l; normal: 5–25 µg/dl, 138–690 nmol/l) with a low-normal UFC, ACTH was elevated (Table 1), and the adrenal glands were atrophic (Fig. 2). Mitotane and metyrapone were discontinued and hydrocortisone was initiated. Over the next 16 months, the signs and symptoms of hypercortisolism resolved.

In October 2010, the patient had recurrent symptoms, elevated UFC and ACTH, and recurrent adrenal gland hyperplasia. Hydrocortisone was discontinued. Imaging studies failed to localize a source of ectopic ACTH and he underwent bilateral adrenalectomy.

Case 2

A 39-year-old man presented with a 6-month history of increasing fatigue, apathy, decreasing exercise capacity, weight gain, and hypertension. The NIH biochemical testing and IPSS suggested EAS. Surgical resection of a right lower lung lesion seen on imaging studies was unsuccessful (Table 1). Treatment with ketoconazole and metyrapone was started (Fig. 1B); metyrapone was later discontinued. On ketoconazole, UFC levels were normal and ACTH levels remained slightly elevated.

In March 2008, the patient discontinued ketoconazole because he wanted to pursue a 'natural' way of life without taking any medications. One year later, off all medical therapy, he reported resolution of signs and symptoms of hypercortisolism except for muscle weakness. Biochemical testing confirmed eucortisolemia (Fig. 1B and Table 1). The patient remained off medications, and reported increasing muscle strength with no evidence of recurrence in October 2011.

Case 3

A 56-year-old woman presented in 2002 with truncal obesity, hirsutism, easy bruising, lower extremity swelling, increasing blood pressure, and low bone

mineral density. At the NIH in 2003, biochemical testing was suggestive of EAS (Table 1). CT scan showed bilateral adrenal hyperplasia. After imaging studies failed to identify the source of ACTH, ketoconazole was initiated. Metyrapone was later added along with dexamethasone using a 'block and replace' strategy (Fig. 1C).

In September 2006, the patient had a sub-normal ACTH level and an undetectable UFC. CT scan showed atrophic adrenal glands. Steroidogenesis inhibitors were discontinued and she was maintained on dexamethasone 250 µg daily. In September 2007, ACTH and UFC were in the low-normal range and the cortisol response to ACTH stimulation was normal; dexamethasone was discontinued. An 8 mm retrocardiac mass was noted on CT and MRI of the chest but was not resected as the patient was eucortisolemic. ACTH and UFC values remain in the low-normal range with no signs and symptoms of hypercortisolism or adrenal insufficiency as of November 2011 (Fig. 1C and Table 1).

Case 4

A 41-year-old man was admitted with sudden onset of altered mental status, hypertension, and hypokalemia in May 2001. Biochemical evaluation confirmed the diagnosis of ACTH-dependent Cushing's syndrome. Imaging studies did not identify a source of ectopic ACTH secretion, but pituitary MRI showed an inferior convexity and asymmetric enlargement of the left side. IPSS suggested a pituitary source of ACTH, but hypercortisolism was not confirmed at the time of IPSS.

Ketoconazole and cyproheptadine were initiated after unsuccessful transsphenoidal surgery (TSS) in October 2001, and cortisol levels decreased. A repeat IPSS performed while off all medications was consistent with a pituitary source of ACTH. However, the patient was not hypercortisolemic at that time (UFC=2 µg/day (5.5 nmol/day) and ACTH=3 pg/ml (0.7 pmol/l); Fig. 1D). After ~6 months, remission, hypercortisolemia and high ACTH levels recurred, consistent with cyclic Cushing's syndrome. For unclear reasons, the patient underwent a second unsuccessful TSS in July 2003.

The patient was then referred to the NIH. Biochemical testing including IPSS performed during hypercortisolism was consistent with EAS (Table 1). Ketoconazole was restarted after imaging studies failed to identify a source of ectopic ACTH. Over the next few years, the patient was maintained on a block and replace regimen with ketoconazole (400–1000 mg/day), cyproheptadine 16 mg/day (continued by his local physician), and low-dose dexamethasone (125 µg/day). On this regimen, UFC remained undetectable, but ACTH ranged from 15 to 66 pg/ml (3.3–14.5 pmol/l).

In June 2009, the patient developed adrenal insufficiency; ketoconazole was discontinued and

Table 1 Clinical and biochemical features of four patients with presumed ectopic ACTH syndrome. To convert ACTH level to picomoles per liter, multiply by 0.2202. To convert urinary free cortisol (UFC) level to nanomoles per day, multiply by 2.759.

Characteristics	Patients			
	1	2	3	4
Age at presentation (years)	42	39	56	41
Sex	Male	Male	Female	Male
Symptoms/signs	Weight gain, moon facies, proximal muscle weakness, easy bruising, and violaceous striae	Fatigue, apathy, weight gain, and hypertension	Truncal obesity, hirsutism, easy bruising, lower extremity edema, and hypertension	Altered mental status, violaceous striae, plethora, moon facies, hypertension, and hypokalemia
Initial labs at NIH				
ACTH (pg/ml; normal: 9–52)	110	143	108.1	71
UFC (µg/day; normal: 8–77)	910	731.5	956.5	670.4
CRH stimulation test	Ectopic	Ectopic	Ectopic	Ectopic
HD DST	Not done	Ectopic	Ectopic	Ectopic
MRI pituitary	5-mm left-sided lesion	No evidence of adenoma	No evidence of adenoma	Inferior convexity, asymmetric enlargement of left lobe, and no adenoma
IPSS venogram	Normal venous anatomy	Left petrosal sinus drained mainly to left vertebral vein; additional samples obtained from jugular and vertebral veins	Normal venous anatomy	No abnormal venous drainage reported
IPSS (peak ACTH IPS/P)	1.5 (109.7/73.6)	1.3 (116/98)	1.5 (92.4/62.4)	1.3 (95.9/73.4)
Anatomical imaging (CT/MRI)	LLL nodule	Questionable lesion anterior to pulmonary vein	Left 8 mm retrocardiac lesion	Paraesophageal lesion, retrocardiac nodule
Functional imaging ^a	Negative	Negative	Negative	Negative
Surgery	Unsuccessful hemihypophysectomy at outside facility; FP LLL nodule surgically removed → scar tissue on pathology	FP RLL lesion, pathology not consistent with neuroendocrine tumor	Surgery not done as patient was eucortisolemic	Two unsuccessful transsphenoidal surgeries done outside → no evidence of ACTH-secreting adenoma
Last follow-up (during remission)				
ACTH (pg/ml; normal: <46)	242	44	20	30
UFC (µg/day; normal: 3.5–45)	13	27	15	14
Duration of remission (months)	16	30	61	15
Possible cause	Toxic effect of steroidogenesis inhibitors/mitotane on adrenal gland	Effect on ectopic tumor vs. cyclic Cushing's syndrome	Effect on ectopic tumor (in remission for 5 years, no history of cyclicity, cyclic Cushing's less likely)	Cyclic Cushing's syndrome

HD DST, High dose (8 mg) dexamethasone suppression test; FP, false positive; LLL, left lower lobe; RLL, right lower lobe; CT, computerized tomography; MRI, magnetic resonance imaging; IPS/P, inferior petrosal sinus to peripheral; UFC, 24-h urinary free cortisol.

^aFunctional imaging by low-dose octreotide scan (LOCT), high-dose octreotide scan (HOCT), and [¹⁸F]-3,4-dihydroxyphenylalanine positron emission tomography (F-DOPA-PET).

Figure 1 (A–D) Twenty-four hour urinary free cortisol (UFC) and ACTH levels over time in (A) case 1, (B) case 2, (C) case 3, and (D) case 4. The X-axis represents time. The primary Y-axis shows ACTH levels (pg/ml) and the secondary Y-axis shows UFC levels (μg/24 h). To convert ACTH level to picomoles per liter, multiply by 0.2202. To convert UFC level to nanomoles per day, multiply by 2.759. The dashed line represents the upper limit of normal for the ACTH assay (46 pg/ml). The dotted line represents the upper limit of normal for UFC (45 μg/24 h). Values where the reference ranges were different have been adjusted for the purpose of combined graphical representation. KTZ, ketoconazole; HC, hydrocortisone; d/c, discontinued; dex, dexamethasone.

dexamethasone increased to 250 μg daily. This remission persisted for ~6 months and was followed by recurrent hypercortisolemia, and ketoconazole was reinitiated.

In June 2010, ACTH was elevated at 60 pg/ml (13.2 pmol/l) with a UFC of 12 μg/day (33.1 nmol/day). Repeat testing after discontinuation of ketoconazole confirmed an elevated ACTH and low-normal UFC. The adrenal glands were of normal size on CT scan and the patient did not have symptoms of hypercortisolism or adrenal insufficiency. An ACTH stimulation test showed borderline peak cortisol response at 17 μg/dl (469.2 nmol/l); dexamethasone was continued. In June 2011, the morning cortisol (3.5 μg/dl (96.6 nmol/l)) and UFC were low with a normal ACTH (Table 1). The cortisol response to ACTH stimulation was normal. The patient has since been maintained on hydrocortisone 10 mg daily and continues to have no signs and symptoms of recurrence as of October 2011.

Discussion

Spontaneous and sustained remission is rarely reported in EAS (7, 8). Beardwell *et al.* described two cases (biochemical testing consistent with EAS but a source of ectopic ACTH not identified) in which hypercortisolism resolved for up to 14 months after treatment with metyrapone. One patient had normal ACTH and cortisol levels 6 months after 2 years of treatment (maximum dose 2250 mg/day). The second patient was in remission for ~14 months after 7 months of treatment with metyrapone 3000 mg daily and prednisolone 7.5 mg daily (7). The authors hypothesized that spontaneous remission in these cases resulted from a direct effect of metyrapone on ACTH secretion from the ectopic tumor or that the tumor required high cortisol levels to secrete ACTH.

Loh *et al.* (8) described a case of EAS due to a pheochromocytoma in which treatment with

Figure 2 CT scan of the abdomen before and during the period of remission in case 1. The left panel (arrow) shows presence of bilateral adrenal hyperplasia in February 2009 when the patient was hypercortisolemic, while the right panel (arrow) shows bilateral adrenal atrophy in the same patient 1 year later (February 2010) during a period of remission.

ketoconazole (400–600 mg/day) for 5 months was followed by spontaneous clinical and biochemical remission for 18 months until resection of the pheochromocytoma.

We describe four cases with presumed EAS where long-term treatment with steroidogenesis inhibitors was followed by remission for 15–60 months. The mechanism of remission in these cases remains unclear. We postulate that they represent a direct effect on the adrenal glands (case 1), and have effects on tumoral ACTH secretion (cases 2 and 3), and on cyclic ACTH secretion (case 4).

In the case of the first patient, treatment with steroidogenesis inhibitors for ~10 years was followed by resolution of hypercortisolemia for ~16 months (Table 1). Remission was associated with an elevated ACTH level, low UFC, and bilateral adrenal atrophy. There are few data on the long-term effects of combined treatment with ketoconazole and metyrapone on the adrenal glands and/or ACTH secretion by a tumor. Mitotane has an adrenolytic effect when given chronically at high doses (> 4 g/day) and this underlies its use in the treatment of adrenal cancer (10, 11). However, the highest daily dose of mitotane used in this patient was 2 g and the duration of treatment was 1.5 years. Although mitotane levels were not measured, it is likely that mitotane, in combination with long-term treatment with ketoconazole and metyrapone, had a direct toxic effect on the adrenal glands, which was reversible after discontinuation of the treatment.

In the second case, treatment with ketoconazole for ~6 years was accompanied by gradually decreasing ACTH levels followed by spontaneous resolution of hypercortisolism. Although we do not have recent biochemical data, the patient reports no signs and symptoms of recurrence and appears to have been in clinical remission for the past 3 years. At the last biochemical evaluation, after taking no medications for 1 year, he had a high-normal ACTH, normal UFC, and decreasing hyperplasia of the adrenal glands on CT scan. The third patient had a response similar to case 2. In her case, treatment with metyrapone and ketoconazole for more than 3 years was followed by remission characterized by low ACTH and cortisol levels and bilateral adrenal atrophy. These data are consistent with

effects on the tumor to decrease ACTH secretion and/or bioactivity.

As suggested previously, an ACTH-secreting tumor might require high cortisol levels for growth and/or hormone secretion (7). Mizoguchi *et al.* reported decreasing ACTH and cortisol levels with metyrapone treatment (1500 mg/day for 2 months) in a boy with an ACTH-producing thymic carcinoid tumor. *In vitro*, tumor cells showed increased proopiomelanocortin (POMC) gene expression when cultured in the presence of 1000 µg/ml of hydrocortisone (12). In another ACTH-producing thymic carcinoid, ketoconazole treatment (800 mg/day for 1 week) led to decreased ACTH and cortisol levels. In culture, ketoconazole reduced ACTH secretion from the thymic tumor cells while cortisol and CRH had no effect, suggesting a direct effect on the tumor cells (13). These cases suggest that long-term treatment with ketoconazole and/or metyrapone may decrease tumoral ACTH secretion, either directly or by decreasing hypercortisolemia. It is not known whether these effects are specific to thymic carcinoids or how often they occur.

Another possible explanation for remission may be altered POMC gene expression and defective ACTH production by the ectopic tumor (14, 15, 16, 17). The tumor may dedifferentiate or develop a transcriptional or posttranscriptional defect leading to production of an ACTH molecule with reduced ability to stimulate adrenal hormonogenesis.

At daily doses of 16–24 mg, the serotonin receptor antagonist cyproheptadine was associated with decreased ACTH and cortisol levels in Cushing's disease patients, with reversal of effect upon discontinuation (18, 19, 20). However, this finding was not consistent and cyproheptadine is not effective in EAS. Case 4 was maintained on cyproheptadine by his local physicians. Given the stable dose of cyproheptadine during ACTH fluctuations, it is unlikely that it played a role in inducing remission in this patient.

Case 4 had a history of two previous 6-month episodes of remission and currently has been in remission for 15 months. Underlying tumor cyclicity is the most likely explanation and his case illustrates the importance of differentiating sustained remission from cyclic Cushing's syndrome. Given previous

reports of recurrent hypercortisolism in cyclic Cushing's syndrome even after 4 years (6), the possibility of cyclic production of ACTH in cases 2 and 3 cannot be completely excluded. Like case 2, case 3 had no history of cyclicity, and has now been in remission for 5 years, making cyclic Cushing's syndrome less likely.

In conclusion, long-term treatment with steroidogenesis inhibitors was associated with prolonged periods of remission in these four cases with presumed EAS. However, this may not be a causal relationship. The exact pathophysiology of remission in these cases remains unclear and may involve several possible mechanisms that require further study. While surgical resection of the ectopic tumor remains the optimal treatment, medical treatment with steroidogenesis inhibitors can be used when a source of ACTH cannot be identified. Combined therapy with multiple steroidogenesis inhibitors has been shown to be effective in both rapid and chronic control of hypercortisolism (10, 21). However, optimal control of hypercortisolism is of paramount importance and bilateral adrenalectomy should be considered in cases where this cannot be achieved on medical treatment. Findings from these four cases suggest that ACTH levels should be measured intermittently or medical therapy should be stopped every 1–2 years to assess whether remission has occurred.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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