

Ectopic Cushing's syndrome with periodic hormonogenesis – a case suggesting a pathogenetic mechanism

V. Estopiñán, C. Varela, P. Riobo, J.R. Dominguez and J. Sancho

Hospital Ramón y Cajal, Crtra. Colmenar Viejo, Km. 9,100, 28034-Madrid, Spain

Summary: We report on a case of ectopic Cushing's syndrome due to a thymic carcinoid tumour with periodic hormonogenesis. Periods of hormonal production averaged 27 days. Prior to bilateral adrenalectomy, mean (s.d) values of ACTH and cortisol were 202.1 (50.3) pg/ml and 46 (14.7) µg/dl, ACTH rising to 3996 ± 425 pg/ml ($P < 0.01$) and cortisol falling to 6.3 ± 1.5 µg/dl ($P < 0.01$) in the immediate postoperative period. During the late postoperative period (2–13 months following surgery) ACTH levels fell to 509.3 (123.8) pg/ml ($P < 0.01$), but remaining even higher ($P < 0.01$) than before adrenalectomy. The pattern of ACTH in the present case suggests the existence of a negative feedback exerted by the cortisol over tumoral ACTH.

Introduction

Periodic hormonogenesis rarely accompanies pituitary and ectopic Cushing's syndrome;^{1–4} its pathogenetic mechanisms are not fully understood. Cyclic variations in symptoms,⁵ and a paradoxical dexamethasone response found by some,⁶ may be related to this phenomenon.

We report on a case of Cushing's syndrome with periodic hormonogenesis produced by an ACTH-secreting carcinoid tumour of the thymus. The existence of a negative feed-back loop of serum cortisol over tumoral ACTH is suggested as a possible explanation for the periodic hormonal release observed in our patient.

Case report

A 39 year old woman with Cushing's syndrome and symptoms dating back 4 months was referred to our hospital. On physical examination, blood pressure was 180/100 mm Hg and the patient showed the characteristic morphological features of hypercortisolism. Significant laboratory values included pH 7.47; sodium 146 mmol/l; potassium 3.2 mmol/l; thyroxine 8.6 µg/dl (normal limits: 4.5 to 12); triiodothyronine 151 µg/dl (normal limits: 85 to 200), and urinary 17-ketosteroids 22 mg/24 hours (normal limits: 4 to 12). Table I shows the basal and dexamethasone suppressed ACTH,

serum and urinary cortisol levels, supporting the previously suspected diagnosis. Mean ± s.d. values of all plasma ACTH and cortisol samples assayed before surgery were 202.1 ± 50.3 pg/ml and 46 ± 14.7 µg/dl, respectively. Cranial X-rays, tomography and computed tomography (CT) did not reveal significant abnormalities. ¹³¹I-19-iodocholesterol adrenal scintigraphy showed bilateral adrenal hyperplasia.

On the basis of raised ACTH levels, lack of suppression on dexamethasone 8 mg and no evidence of pituitary tumour a clinical diagnosis of an ectopic ACTH-secreting tumour was made. Thoracoabdominal CT, chest tomography, upper gastrointestinal series, barium enema, bronchoscopy and thyroid scintigraphy were all negative. Phaeochromocytoma and a serotonin-producing tumour were both excluded after repeated testing for urinary catecholamines and 5-hydroxyindoleacetic acid. Figure 1 illustrates serum and urinary cortisol levels, showing periodic hormonogenesis and a paradoxical response to dexamethasone. Statistical evaluation of the results was performed with a Newman-Keuhl test.

Bilateral adrenalectomy was performed 2.5 months after admission due to the progressive worsening of the clinical condition and corticosteroid substitution therapy was initiated. Mean (± s.d.) values of serum ACTH and cortisol from 3 serial determinations performed between the 11th and the 18th postoperative day were 3996 ± 425 pg/ml and 6.3 ± 1.5 µg/dl respectively ($P < 0.01$ in both cases). During the ensuing 12-month period 8 determinations of ACTH and cortisol were made. Plasma ACTH fell to 509.3 ± 123.8 pg/ml ($P < 0.01$ vs both presurgical

Correspondence: V. Estopiñán García, M.D., Servicio de Endocrinología, Hospital Ramón y Cajal Crtra. Colmenar Viejo, Km. 9,100, 28034-Madrid, Spain
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Table I Basal and dexamethasone-suppressed (Dexa 2 mg*, Dexa 8 mg†) serum and urinary cortisol, and serum ACTH levels

	Serum cortisol ($\mu\text{g/dl}$)				Urinary cortisol ($\mu\text{g}/24\text{ h}$)			ACTH (pg/ml)			
	Basal		Dexa 2 mg	Dexa 8 mg	Basal	Dexa 2 mg	Dexa 8 mg	Basal			
	0800 h	20.00 h						0800 h	20.00 h	Dexa 2 mg	Dexa 8 mg
Patient	34	31	48	68	660	5164	7692	129	156	178	226
Control	9-24	3-9	<5	<5	<150	<30	<30	<100	<100	<30	<30

*0.5 mg/6 h for 48 h. †2 mg/6 h for 48 h.

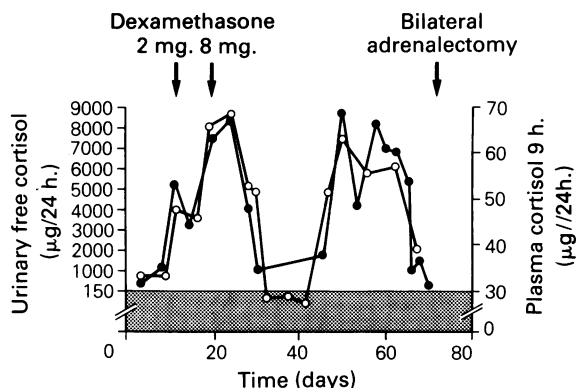


Figure 1 Serum (○—○) and urinary (●—●) cortisol concentrations showing periodic hormonogenesis.

and immediate postsurgical periods), whereas serum cortisol levels were $6.2 \pm 1.2 \mu\text{g/dl}$ ($P < 0.01$ vs presurgery). Figure 2 shows mean \pm s.d. values of serum ACTH and cortisol at preoperative, immediate postoperative and late postoperative periods. Cranial and thoracoabdominal CT were repeatedly negative.

Three years after surgery, enlarged supraclavicular lymph glands developed revealing metastatic extension from a carcinoid tumour on histological examination. The tumour was thereafter localized in the thymus by a total body CT scan. A palliative surgical procedure ensued and postoperative mediastinal radiotherapy and chemotherapy were initiated. Immunohistochemical studies of the tumour demonstrated the presence of cells containing ACTH granules.

Discussion

Periodic hormonogenesis is a rare finding in both central and ectopic Cushing's syndrome. Adrenal adenomas do not show this phenomenon, although clinical fluctuations may be observed.⁷ Cyclic hormonal production intervals in the literature range

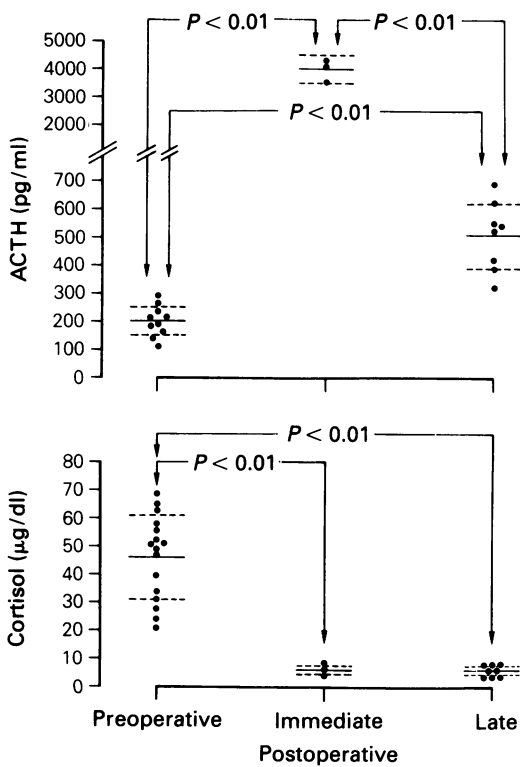


Figure 2 Plasma ACTH and cortisol at preoperative, immediate postoperative and late postoperative periods.

from 6 days,⁴ to 85.5 days;³ in our patient, episodic ACTH release occurred every 27 days.

The aetiology of the periodic hormonogenesis in ectopic Cushing's syndrome is not fully understood. A possibility is that the increase in hormone production follows the tumoral growth, while the decreased hormonal production would be explained by patchy tumoral necrosis.¹⁸ However, hormonal secretion under these conditions would be of intermittent, rather than cyclic nature and histological examination

has failed to demonstrate tumoral necrosis in some cases.¹ Another possibility is the existence of a negative feedback system from cortisol over tumoral ACTH. Rapid tumoral growth occasionally seen after adrenalectomy⁹ favours this hypothesis. Further supporting these data, we observed a substantial increase in plasma ACTH after eliminating endogenous cortisol through a bilateral adrenalectomy. Later on post-operative ACTH concentrations decreased, though never achieving pre-adrenalectomy values.

Massive ACTH secretion after surgical removal of both adrenal glands could be related to the release of the tumoral ACTH stores, not inhibited by high serum cortisol concentrations. However, plasma ACTH

values from a few months later would more likely reflect the 'de novo' synthesis of this peptide by the primary tumour.

Periodic hormonogenesis adds some difficulty in the aetiological diagnosis of Cushing's syndrome, because the results of the stimulatory and suppressive tests depend on the time at which they are performed. In our patient, the paradoxical dexamethasone response observed probably reflects that the test was done during the ascending slope of the hormonal cycle. Total body venous catheterization, searching for an ACTH gradient,¹⁰ may be a useful diagnostic tool in the localization of Cushing's syndrome of unknown origin.

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