

# A rare case of Cushing syndrome by cyclic ectopic-ACTH

*Um caso raro de síndrome de Cushing associada a ACTH-ectópico cíclico*

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## SUMMARY

ACTH-dependent Cushing syndrome (CS) due to ectopic ACTH production is most times difficult to manage. The identification of the source of ACTH may take many years. Surgery or chemotherapy for the primary tumor is not always possible. Control of Cushing symptoms is many times achieved using medication, or bilateral adrenalectomy in refractory cases. This case presents a Brazilian male who showed severe hypertension, mood changes, muscle weakness, darkening of skin, and increased abdominal fat. An investigation for Cushing syndrome was carried out and, after a four-year follow-up, a carotid glomus tumor (chemodectoma) was confirmed, a rare ectopic ACTH-producing tumor. Besides, the patient presented cyclic Cushing syndrome that was exacerbated by diverticulitis episodes. This case presents interesting pitfalls on diagnosis and management of ACTH-dependent CS. This is the only report of a chemodectoma that produced ACTH in the literature. *Arq Bras Endocrinol Metab.* 2012;56(5):324-30

## SUMÁRIO

A síndrome de Cushing ACTH-dependente causada por produção ectópica de ACTH é, muitas vezes, difícil de diagnosticar e conduzir. A identificação da fonte produtora de ACTH pode demorar muitos anos. A cirurgia ou quimioterapia para o tumor primário nem sempre é possível, sendo o controle do hipercortisolismo alcançado com uso de fármacos ou adrenalectomia bilateral, nos casos refratários. Este caso apresenta um homem com hipertensão grave, mudança de humor, fraqueza proximal, escurecimento da pele e aumento de gordura abdominal. A investigação para síndrome de Cushing foi feita e, após quatro anos de acompanhamento, confirmou-se um tumor de glomus carotídeo (quemodectoma), causa rara de tumor secretor de ACTH. Nesse período, o paciente apresentou síndrome de Cushing cíclica, exacerbada por crises de diverticulite. O caso ilustra pontos importantes no diagnóstico, no acompanhamento e na condução da síndrome de Cushing ACTH-dependente, sendo este o único caso de tumor de glomus de carótida produzindo ACTH descrito na literatura médica. *Arq Bras Endocrinol Metab.* 2012;56(5):324-30

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## INTRODUCTION

Numerous types of endocrine and non-endocrine tumors acquire the ability to secrete substances that are not usually produced by the normal tissue from which the tumor is originated (1). Various solid tumors, mainly of neuroendocrine origin, are as well recognized as ACTH-secreting ones, causing ectopic-ACTH secretion (EAS) (2). Either benign or malignant tumors may be the cause of EAS. Malignant tumors, nevertheless, have been associated with extremely high circulating ACTH and cortisol levels, and short duration of symp-

toms of Cushing syndrome (CS) besides atypical clinical phenotype, when compared with pituitary-dependent Cushing (1). Identification of the source of ACTH can be challenging, as sometimes the primary lesion is not identified even after prolonged and repeated follow-up (3). When the patient has CS characteristics, with tests indicating an ectopic source and the primary tumors are not identified, it is called occult EAS (1).

Various tumors may cause EAS, with the most frequent being small cell lung carcinoma; carcinoid tumors (especially of the lungs, thymus and gastrointestinal tract); islet cell tumors, pheochromocytoma;

medullary thyroid carcinomas. Other miscellaneous tumors associated with EAS are paragangliomas, neuroblastomas, as well as prostate, breast, kidney, stomach, ovary, colon, anorectal, and other cancers (1).

Diagnosis of ACTH ectopic secretion involves two basic steps that cannot be omitted to prevent misdiagnosis: confirmation of hypercortisolism and determination of its etiology (differential diagnosis) (4). After confirmation of hypercortisolism in ACTH-dependent matter, bilateral sinus sampling (BIPSS) is the best single test to differentiate between a central and a peripheral source of ACTH (2,5). Once EAS is confirmed, identification of the site of the primary tumor may begin with chest high-resolution computerized tomography (CT) scan. If results are normal, extensive abdominal CT should be carried out (4). In the case of negative scans, somatostatin receptor scintigraphy (SRS) or fluorine-18-fluorodeoxyglucose positron emission tomography scan ([18-F]-FDG-PET) may be used. The rationale for SRS is the presence of large number of high-affinity somatostatin receptors in many neuroendocrine tumors. The potential advantage in relation to conventional radiology is that it gives information about the whole body, enabling

primary and metastatic lesions to be visualized (4). Fluorine-18-fluorodeoxyglucose PET is widely used to identify malignant (high metabolism) tumors. In small series, [18-F]-FDG-PET failed to identify tumors that were occult on CT or magnetic resonance imaging. It seems to confer no benefit in the detection of ectopic ACTH-secreting tumors beyond conventional imaging (6).

## CASE REPORT

A 49-year-old Brazilian male presented with severe hypertension, mood changes mainly characterized by instability, alternating between aggressiveness and depression. Progressive muscle weakness, darkening of skin, and increased abdominal fat were observed. His symptoms and laboratory tests confirmed an ACTH-dependent Cushing syndrome (CS) (Table 1, Figure 1). Chest X-ray and computed tomography scan (CT), as well as pituitary CT and magnetic resonance imaging (MRI) were normal. Abdominal CT revealed bilateral adrenal enlargement. Bilateral simultaneous inferior petrosal sinus sampling after desmopressin (DDAVP) stimulus (BIPSS) suggested ectopic ACTH production (Table 2).

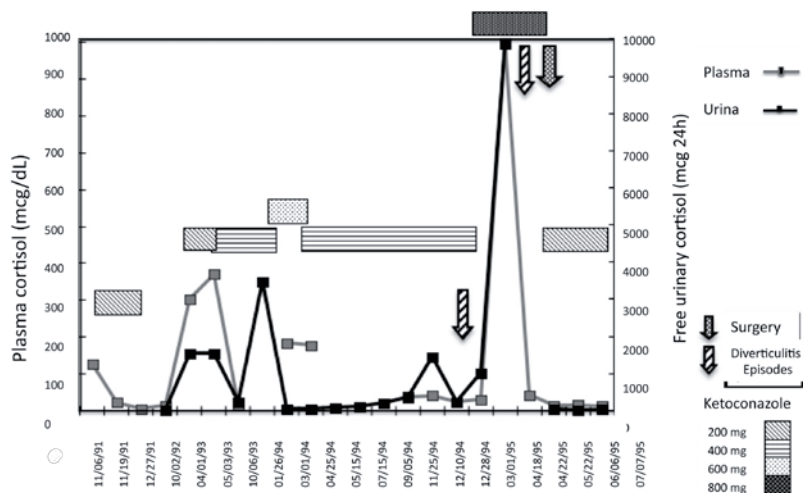
**Table 1.** Laboratory results and corresponding clinical manifestations during the first four years of disease

Date	06/11/91	2/10/92	01/04/93	03/05/93	28/02/94	25/04/94	10/12/94	18/01/95	18/04/95
Condition				High-dose dexamethasone test					
Plasma Cortisol (8h) mcg/dL* (NR 5 -25)	125	13.8	<b>303</b>	370	184	177	23.9	-	41.7
Free Urinary Cortisol (mcg) 24h		10.4	<b>1540</b>	1546	-	-	1444	230.6	9860
ACTH (pg/mL) <sup>#</sup> (NR < 160)		124	113	238	238	-	-	397	
K <sup>+</sup> mEq/L <sup>**</sup> (NR 3,5 - 5,3)		5.0		3.5	3.5	-	-	-	2.4
Medication (ketoconazole)		Discontinued since February/1992	400 mg	400 mg	600 mg	Reduced to 200 mg	400 mg	400 mg	800 mg
Clinical features	Urinary infection Oral candidiasis	Assymptomatic No Cushing features			Severe myopathy Anorexia Anxiety Cutaneous hyperpigmentation	Asymptomatic Improvement of 'Cushing' symptoms	Ciprofloxacin + Metronidazole		Garamycin + Metronidazole (inpatient treatment) Hemicolecotomy
Others		-	Low dose dexamethasone overnight suppression test Plasma cortisol 28,5 ng/mL (5-25)						

\* Chemiluminescent immunoenzymatic assay.

<sup>#</sup> Immunoradiometric (IRMA) assay.

<sup>\*\*</sup> Selective Electrode.



**Figure 1.** Plasma and free-urinary cortisol variations in the first three years of CS onset (before identification of primary tumor site identification).

**Table 2.** Patient's bilateral simultaneous inferior petrosal sinus sampling (BIPSS) after DDAVP stimulation

	ACTH measurement* after DDAVP stimulus during bilateral simultaneous inferior petrosal sinus sampling (BIPSS)	
	Right	Left
Central	675 pg/mL	665 pg/mL
Peripheral Jugular Vein	870 pg/mL	880 pg/mL
Subclavic vein	985 pg/mL	795 pg/mL

\* Immunoradiometric (IRMA) assay.

Interestingly, this patient presented a quite variable level of serum cortisol and free urinary cortisol that were followed by different symptoms of hypercortisolism. Several times, episodes of diarrhea, fever and abdominal pain preceded worsening of hypercortisolism symptoms. During these episodes, an astonishing increase in serum and urinary cortisol were noticed (such as 9,850 mcg free urinary cortisol/24h, as shown in Table 1). In contrast, antibiotics plus ketoconazole therapy was always accompanied by a sharp decrease in cortisol levels, amelioration of Cushing stigmata, even with disappearance of hyperpigmentation. Diverticulitis was suspected, and later on, diagnosed. In general, ketoconazole in a daily doses between 200 and 600 mg controlled hypercortisolemia until normalization. Ketoconazole had to be discontinued many times due to symptoms of adrenal insufficiency.

During four years, this patient was followed up and kept showing periodic hypercortisolism. Then keto-

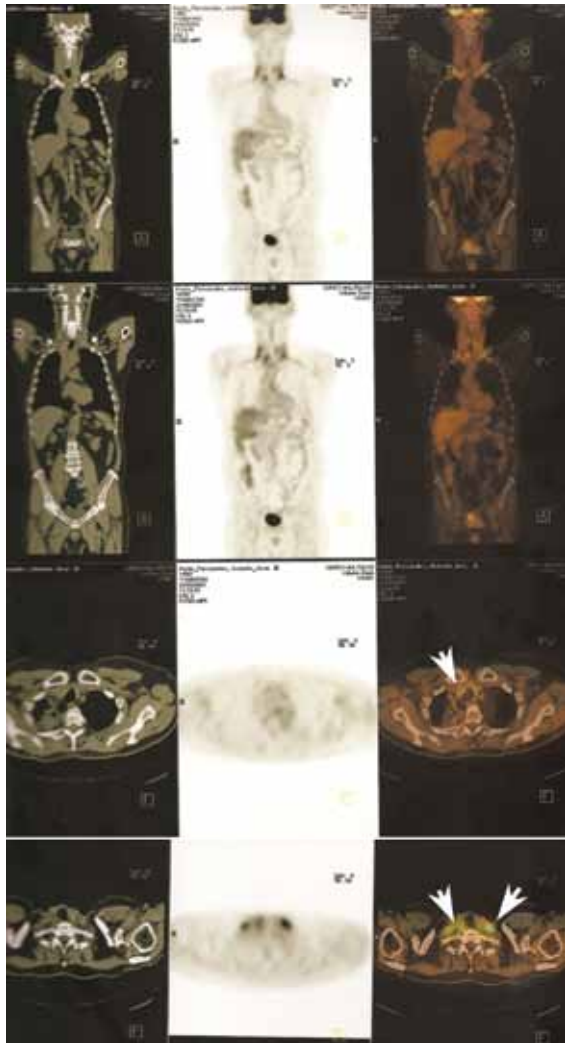
conazole was reintroduced and periods of quite normal cortisol status followed. MRI or CT scans were performed every 6 months and did not succeed in locating the source of ACTH. Colonoscopies were done twice. Few intestinal polyps were found and removed. No malignancy was demonstrated, and immunohistochemistry showed no evidence of ACTH production. Finally, hemicolectomy for diverticular disease was performed, and no tumor was found.

The patient was sent to the endocrine department of the National Institutes of Health, Bethesda, Maryland, in the United States, to perform an Octreoscan. Results were suggestive of neuroendocrine cervical tumor at the left ganglionic chain adjacent to the carotid bifurcation sinus. Operation was performed and histopathology showed a neuroendocrine tumor of carotid glomus invading local lymph nodes and left parathyroid, and positive for ACTH and cromogranin A. After surgery, Cushing symptoms disappeared and cortisol levels were normalized. Adjuvant radiotherapy was carried out. Reoperations for disease recurrence were performed after four and six years. The last one found a new tumor onset in the contralateral ganglion chain, posterior to the right carotid, invading the jugular vein, with ipsilateral involvement of the vagus nerve. The tumor was positive in [18-F]-FDG-PET (Figure 2). Chemotherapy was performed for recurrences in the following six years, with etoposide/cisplatin, interferon, and octreotide LAR, respectively, plus ketoconazole. During the last year of evolution (eighteen years

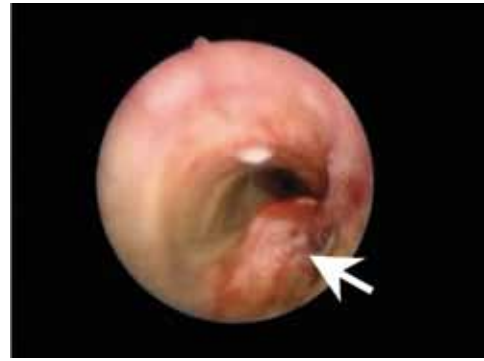
after the initial diagnosis) the therapy protocol barely helped to control symptoms. Bilateral adrenalectomy was programmed.

In the end, patient developed bilateral pneumonia complicated by sepsis. In this setting, extremely high cortisol levels resulted in severe hypertension, hypokalemia, hypomagnesemia, hypocalcemia, and hyperglycemia. Ketoconazole therapy was attempted to control CS symptoms but, at this time, it resulted in severe liver toxicity (ALS and ALT increased 100 times above normal range). After improvement of the septic state, videoendoscopic bilateral adrenalectomy was successfully carried out. During anesthesia procedures tracheal invasion by the tumor was documented (Figure 3).

The patient died from a massive hemorrhagic episode due to carotid artery fistulae to the trachea.



**Figure 2.** Fluorodeoxyglucose positron emission tomography scan (FDG-PET CT) demonstrating tumor recurrence (18).



**Figure 3.** Bronchoscope image showing invasion of the posterior wall of the trachea by the tumor (arrow; kindly provided by Dr. Fernando Pacheco).

## DISCUSSION

This case presents an ACTH-dependent CS with a cyclic pattern, most of the time related with intestinal infection episodes. This pattern kept the medical team's attention on the intestinal tract, which emphasizes the difficulties that may be associated with the investigation and management of ectopic ACTH-producing tumors. Besides, as far as we are concerned, a chemodectoma producing ACTH in a cyclic fashion has never been described before in the literature.

Cyclic CS is a rare disorder, characterized by repeated episodes of cortisol excess interspersed by periods of normal cortisol secretion (7). The so-called cycles of hypercortisolism can occur regular or irregularly with inter-cyclic phases ranging from days to years. To formally diagnose cyclic CS, three peaks and two troughs of cortisol production should be demonstrated (7). In a review of cyclic CS cases in the literature published in English from 1960 to 2007, 65 cases were found (7). Cushing's disease (CD) was the underlying cause in 54%, ectopic secretion of ACTH in 26%, and primary adrenal CS in 11% of these cases of cyclic Cushing. Considering CS in general, the corresponding prevalence, reported in the literature is 68%, 12%, and 20% respectively (8). Thus, the occurrence of ectopic ACTH syndrome seems to be more frequent in patients with cyclic CS (7).

Tumors originating from parasympathetic cells at carotid glomus are recognized as head and neck paragangliomas (HNPGLs) or chemodectomas, because parasympathetic cells are chemical sensor cells. As for CS caused by chemodectomas, this is the first case reported, to the best of our knowledge. Furthermore,

carotid body tumors are rare. They may be single, bilateral or multicentric. In a review of 88 familial and 835 non-familial cases, bilateral disease was more frequent in the familial (31.8%) than in the non-familial (4.4%) cases (9).

Chemodectomas are usually benign and slow-growing tumors of the parasympathetic ganglia with an incidence of roughly 1:30,000 – 1:100,000 cases in the overall population. Risk factors for HNPGLs include conditions associated with chronic hypoxia, such as living at a high altitudes, respiratory or heart diseases with chronic arterial hypoxemia, which were not the case with this patient. However, in 7%-10% to 50% of the cases, genetic predisposition has been suspected based on positive family history and/or development of bilateral or multiple primary tumors (10-12); more recently, the proportion of tumors caused by an inherited predisposition has been identified as close to 35% (13).

Hereditary susceptibility to HNPGLs was recognized at least two decades ago. It enabled the identification, using linkage analysis, of three loci on chromosome 11 and 1, named PGL1 on 11q23, PGL2 on 11q11.3, and PGL3 on 1q21-23 (14). We could not attribute a hereditary background to this patient, but a mutation at the SDH loci is possible, considering the malignant characteristic and bilateralism. SDH is an enzyme complex composed by four subunits encoded by four nuclear genes (SDHA, SDHB, SDHC and SDHD), located on chromosomes 1, 5 and 11. Heterozygous mutations of the last three subunits have been associated with a genetic predisposition to HNPGLs and adrenal/extra-adrenal pheochromocytomas (PHEOs) (15,16). Therefore, an autosomic dominant mutation on succinyl dehydrogenase gene (SDH) was suspected to be responsible for both the bilateral and malignant characteristic of our patient tumor. However, genetic testing for this mutation was not available at that time.

The association between chemodectoma and pheochromocytoma is well recognized (17). In fact it is recommended that all patients with chemodectomas should be screened for PHEOs. Urinary catecholamine in the present case was always negative, as well as serum chromogranin A.

Ectopic production of ACTH by chemodectomas is a rare event. As far as we know, there is only one case reported in literature associating a neck paraganglioma with CS (18). Another patient with CS has been reported, in whom resection of a chemodectoma following

bilateral adrenalectomy resulted in decreased ACTH levels. Nonetheless, there was no evidence of cyclic ACTH production (19).

Identification of the primary tumor responsible for the ectopic ACTH production may be troublesome. CT, PET-FDG, and octreoscan have equal, but low sensitivities for this purpose. They must complement each other in difficult cases. A variety of factors may influence the ability of FDG-PET to locate a tumor. Increased metabolic rate and glucose transport through tumor cell membranes are necessary for increased uptake of FDG (20). Classically, tumors from the carotid body are PGLs, predominantly with chief cells delimited by trabeculae, and present low mitotic index. Theoretically, PET-FDG is not a good method for the screening and follow-up of this kind of tumor. Our patient, on the other hand, had a very aggressive and persistent tumor that, despite long term evolution, was invasive and very avid for FDG.

## TREATMENT AND MANAGEMENT

The choice of treatment for ectopic ACTH syndrome depends on tumor identification, location, and classification. The most effective treatment option is surgical resection and cure, although this is not always possible (e.g. in metastatic disease or in the case of occult tumors). Tumor-directed therapy involves an individualized approach, and can include somatostatin analogues, systemic chemotherapy, interferon- $\alpha$ , chemoembolization, radiofrequency ablation, and radiation therapy (21-24). In the present case, surgery for tumor resection was attempted three times, but the tumor was locally invasive since diagnosis. Radiotherapy was also attempted, with poor response and hypoparathyroidism as a consequence. Chemotherapy with both anti-neoplastic drugs and, later on, somatostatin analogues (octreotide-LAR) was carried out during follow-up.

Hypercortisolemia-directed therapy, that is, medical therapy to block cortisol production or bilateral adrenalectomy, is warranted in patients with ectopic ACTH syndrome who have failed primary surgical therapy. It is also used in patients with occult ectopic ACTH syndrome (EAS), or patients with malignant disease with metastases or very severe symptoms of CS (25,26). Adrenal-directed therapy (steroidogenesis inhibitors) may be highly effective, but it does not treat the underlying tumor or restore normal hypothalamus-pituitary-adrenal axis dynamics (27-31).

Most studies with steroidogenesis inhibitors have been carried out with metyrapone and ketoconazole (27-31). Metyrapone treatment leads to marked inhibition of aldosterone biosynthesis, and accumulation of aldosterone precursors with weak mineralocorticoid activity. Blood pressure levels and electrolyte balance vary individually with the degree of aldosterone inhibition and 11-deoxycorticosterone (DOC) stimulation. Adverse effects due to increased DOC levels (hypokalemia, edema, hypertension) are infrequent (31). Metyrapone is not commercially available in Brazil. Ketoconazole is usually the first choice. Widely available, and generally well tolerated, it was our choice to control Cushing symptoms since the beginning of the case. Mild elevation in liver enzymes (up to three-fold normal levels), which are transient, is not a contraindication to medical therapy with ketoconazole. Liver function should be carefully monitored because of the rare complication of liver failure (32). In our case, for several years, this drug was well tolerated and actually controlled hypercortisolemia. However, on the very last days, liver enzymes rose 100 times above the normal range. It is possible that drug interaction contributed to this outcome.

Mitotane (*o,p'*-DDD) may prove to be highly effective in the long-term suppression of hypercortisolism in the majority of patients with ACTH-dependent CS, because of its specific adrenolytic action. However, the onset of its action is slow (weeks or months), and the adverse effects associated with mitotane therapy (mainly digestive and neurological) require careful monitoring of drug levels. This kind of therapy is routinely used in only a few centers (33), and is more useful for adrenocarcinoma treatment.

Intravenous etomidate therapy may be considered in situations where rapid control of cortisol levels is required and oral therapy is not advisable (34). It can be a bridge to definitive treatment, such as surgery for primary tumor, bilateral adrenalectomy, or until the action of a slow-onset adrenolytic agent or steroidogenesis inhibitor starts.

Neuroendocrine tumors that cause EAS often express functional somatostatin (SS) receptors (35). Smaller studies and case reports have been published on the use of octreotide in patients with EAS. Interestingly, octreotide was efficacious in lowering cortisol levels in a significant number of these patients, as opposed to studies performed in patients with CS (36,37). This finding can be justified by the fact that many patients with EAS have positive lesions on <sup>111</sup>In-pentereotide scan

(Octreoscan), whereas most patients with CS do not (38). The observation that many of the EAS-producing neuroendocrine tumors have functional sst2 receptors, despite chronic hypercortisolism, could be explained by aberrant glucocorticoid receptor signaling in these tumor cells. One of the main concerns with the use of SS analogs in EAS, however, appears to be the long-term control of hypercortisolism. Although initial responses to octreotide are frequent, these are not always sustained, and unresponsiveness to treatment is common, due to a number of possible mechanisms of tachyphylaxis (39). A trial with octreotide-LAR was also done in the presented case; nonetheless, Cushing symptoms were not properly controlled.

Our patient stayed under ketoconazole treatment for many years, with good control of Cushing symptoms. The only reasonable option, considering tumor treatment failure and late ketoconazole adverse effects, was bilateral adrenalectomy.

## CONCLUSION

ACTH-dependent Cushing syndrome due to ectopic ACTH production most of times is difficult to manage. The identification of the source of ACTH may take many years until final diagnosis.

We report a case of a cyclic ACTH-dependent Cushing syndrome due to a chemodectoma located in the carotid glomus. A chemodectoma producing ACTH, as far as we know, has never been described before in the literature. Experience acquired with this patient suggests that a practitioner facing an ACTH-dependent Cushing syndrome must invest all available resources in shortening ACTH production site location. Several distinct locations, and association with others neuroendocrine tumors warrants such a strenuous effort. Moreover, therapy directed to the ACTH source seems obvious, but not always possible or curative. Meanwhile, ketoconazole to control hypercortisolism demonstrated to be efficacious and safe for several years, underscoring its appropriateness. Determination of the genetic profile looking for SDH mutations is a new tool, which might be considered for prognostic stratification.

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