SAR Journal of Medical Case Reports

Abbreviated Key Title: *SAR J Med Case Rep*
Home page: https://sarpublication.com/journal/sarjmcr/home
DOI: 10.36346/sarjmcr.2023.v04i03.002

ISSN 2707-7780 (P)
ISSN 2709-6947 (O)

Case Report

Ectopic Cyclic Cushing's syndrome, A Diagnostic Challenge: A Case Report

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Article History: | Received: 30.05.2023 | Accepted: 05.07.2023 | Published: 13.07.2023 |

Abstract: *Introduction:* Cyclic Cushing's syndrome is a not widely known pathology with low incidence; however, an increase in the number of cases has been observed in recent years. The intermittent clinical symptoms and discordant laboratory results make it a complicated diagnosis; therefore, close follow-up is crucial. We describe a case of ectopic cyclic Cushing's syndrome in a woman in her seventies who presented weight gain, proximal myopathy, moderate hypokalemia and uncontrolled hypertension; in the first evaluation hypercortisolism was found, however, 2 months later cortisol presented normal levels. Subsequently, a close follow-up was carried out and the study protocol was continued once the presence of 3 peaks and 2 valleys was demonstrated, obtaining compatible values for ectopic ACTH-dependent cyclic Cushing's syndrome. In thoracoabdominal MRI a spiculated lesion was found in the left basal lung field surrounding 25% of the aorta. Due to the location of the lesion, the patient refused surgical treatment, being currently under adequate control with the use of ketoconazole and octreotide injections. *Conclusions:* The possibility of cyclic Cushing's syndrome diagnosis should be kept in mind in those patients with symptoms suggestive of Cushing's syndrome that remit sporadically and whose laboratory studies show intermittent results of hypercortisolism and normocortisolism, since early identification allows opportune treatment and therefore better prognosis.

Keywords: Cushing's syndrome, cyclic, ectopic, case report, somatostatin analogues.

INTRODUCTION

Cyclic Cushing's syndrome is a rare disease characterized by episodes of hypercortisolism alternating with periods of normocortisolism, which may occur at regular or irregular intervals ranging from days to months (from 12 hours up to 85 days). Fifty four percent of the cases originate from an ACTH-producing pituitary adenoma, 26% secondary to an ectopic ACTH-producing tumor and 11% from an adrenal tumor, the rest being of unknown etiology [1,2]. It presents more frequently in women with a 1:3 male to female ratio, predominantly in the fifties to sixties [2]. The signs and symptoms of cyclic Cushing's syndrome may be fluctuating or permanent. The oscillating clinical picture and discrepant biochemical findings, make diagnosing cyclic Cushing's syndrome challenging [3].

Patients with cyclic Cushing's syndrome must meet the following diagnostic criteria:

1) Demonstrate at least 3 periods of hypercortisolism (peaks) interspersed with 2 periods of normocortisolism (valleys).
2) Clinical manifestations compatible with Cushing's syndrome, which may disappear or reappear spontaneously.
3) Imaging studies showing adrenal, pituitary or ectopic lesions.
4) To rule out that patients are using corticosteroids exogenously and to exclude non-neoplastic Cushing's syndrome (obesity, depression and alcoholism) [4], treatment is focused according to the etiology since it must be directed against the triggering cause.

CASE REPORT

A 61-year-old woman with a 5-year history of arterial hypertension diagnosis under treatment with losartan 50 mg every 24 hours and metoprolol 50 mg every 12 hours, 1-year of osteoporosis diagnosis under treatment with calcitriol 0.25 mcg every 24 hours and risedronic acid 5 mg every 24 hours.

Table 1: Confirmatory tests for hypercortisolism

Date	28/01/2011
Cortisol	31.5 ug/dl
ACTH	94.1 pg/ml
Urinary cortisol	1035 µg/24 h

Her condition began in January 2010 with an approximately 10 kg weight gain, associated with pelvic limbs edema; later she presented progressive weakness of proximal predominance, until it became disabling, requiring hospitalization where moderate hypokalemia was documented, she was discharged with potassium salts. Two months after hospital admission, she presented remission of symptoms (8 kg estimated weight decrease, reduction of edema, improvement of blood pressure control); as part of the diagnostic approach, a hormonal profile was requested (Table 1 - 3) with altered results. For this reason, she was directed to the endocrinology service for evaluation.

Table 2: Initial pituitary profile laboratory results

Date	**4/01/2011**
TSH	2.1 mU/L
T3T	72 ng/dl
T4T	7.5 µg/dl
FSH	0.8 U/L
LH	0.1 U/L
Prolactine	36.1 ng/ml
Progesterone	1.8 ng/ml
Estradiol	13.1 pg/ml
Cortisol	55 µg/dl

Table 3: Follow-up laboratory results one month after the initial determination

Date	**8/02/2011**
Cortisol LDDST	42.4µg/dl
ACTH	216 pg/ml

She was examined in the endocrinology outpatient clinic for the first time on April 15, 2011, where the laboratory studies were previously shown, there was observed serum and urinary cortisol elevation, as well as persistence of hypercortisolemia after the low dose dexamethasone suppression test (LDDST), confirming the diagnosis of Cushing's syndrome. According to ACTH levels, which were found to be above 15 pg/ml, ACTH-dependent hypercortisolism was considered. During the patient's follow-up, serum cortisol was requested with LDDST, achieving a suppression of 1.58 µg/dl and urinary free cortisol (UFC) 53 µg/24 h, finding discordance with the values observed in the initial evaluation. She was admitted to hospitalization for case protocolization in August 2011, obtaining serum cortisol with LDDST 26 µg/dl and nocturnal cortisol (at 11 pm) 29.7 µg/dl; as well as ACTH levels 77 pg/ml. Because of the results, we proceeded to perform the high doses of dexamethasone suppression test (HDDST), obtaining the results reported in Table 4.

Table 4: Differential diagnosis of ACTH-dependent Cushing's syndrome

Basal cortisol	30 µg/dl
Cortisol (HDDST)	17 µg/dl
Suppression percentage	43%

The patient was discharged with the diagnosis of cyclic Cushing's syndrome probably. As part of the follow-up, she was evaluated in the endocrinology outpatient clinic in December 2011 presenting new weight gain, but without classic stigmata of Cushing's disease, with the following control laboratory studies: morning serum cortisol 5 µg/dl and ACTH 12 pg/ml. To confirm the diagnostic suspicion previously raised, a new hospitalization was decided for infusion with 7 mg of dexamethasone in August 2012 with no suppression. Given the persistence of hypercortisolism, in September 2012 a 48-hour dexamethasone purification was performed (dexamethasone 2 mg every 6 hours) achieving 44% suppression, (Table 5).

Table 5: Infusion and suppression tests with dexamethasone

	Infusion with 7 mg of dexamethasone		48 h Dexamethasone suppression test
Basal cortisol	35.5 µg/dl	Basal cortisol	39.7 µg/dl
5h later	38.2 µg/dl	Post-test cortisol	22 µg/dl
7 h later	36.7 µg/dl	Suppression percentage	44%

A thoracoabdominal MRI was requested, which showed a spiculated image in the left basal lung field with 25% involvement of the aorta, which is hypointense in T1 and hyperintense in T2 sequence, measuring 4 x 4 mm in its largest diameters laterolaterally and dorsoventrally. In April 2013 she was admitted to the emergency department for an episode of hypokalemia that responded after the

administration of intravenous potassium chloride (KCl); during this hospitalization cortisol was determined with LDDST 30.7 µg/dl and urinary cortisol 31.9 µg/24 hours. She was discharged satisfactorily after 3 days with potassium salts and ketoconazole. In October 2013 she underwent a gammagram with Octreoscan indium 111 without abnormal areas, continuing with the same treatment. In November 2013, she presented a new hypokalemia crisis with normal serum cortisol levels, ketoconazole was discontinued, while hydrocortisone was started. However, that December she presented a Cushing's syndrome reactivation, so ketoconazole was restarted as tolerated.

In January 2015, PET CT showed somatostatin receptor uptake in the lung and mesentery compatible with neuroendocrine tumor (Figure 1); a couple of months later, treatment with somatostatin analogues (octreotide) was started with a dose of 20 mg intramuscular every 4 weeks.

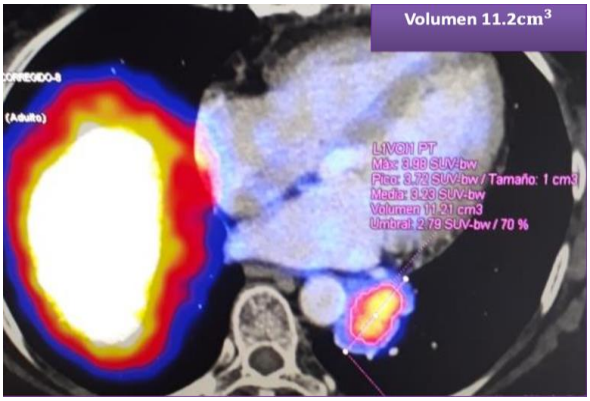

Figure 1: PET/CT Gallium 68 DOTA TOC 2015 left posterobasal lung tumor 46x29x37 mm, with SUVmax 3.9 in contact with the aortic wall and pericardium

In April 2016, surgical intervention was proposed for resection of abnormal lung tissue previously evidenced in PET CT with the purpose of achieving cure of the disease, however, she rejected this therapeutic option due to high surgical risk. In order to evaluate the response to treatment with somatostatin analogues, a control PET CT scan was requested in December 2016, which showed a decrease in the size of the lung lesion compared with the previous study (Figure 2).

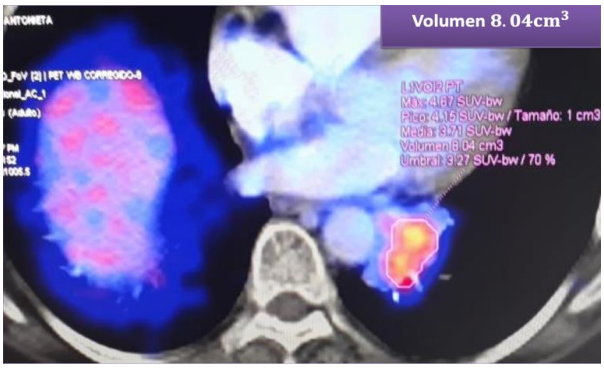

Figure 2: PET/CT Gallium 68 DOTA TOC 2016 tumor presented a volume of 8.04 cm³ corresponding to a reduction in size of 28%

In the following months she has continued with periodic evaluations by the endocrinologist with morning serum cortisol and ACTH; in addition, education and orientation about the disease has been provided to the patient and family members. Due to the presence of hypocortisolism, ketoconazole has to be suspended and prednisone should be started as an hormone replacement. On the other side, treatment with ketoconazole would be restarted when disease activation appears, manifested by increased blood pressure, weight gain and Cushing's stigmata. In September 2018 PET-CT 68 GA-DOTANOC was performed which reported left lung mass with radiotracer decrease in 13% corresponding with stable disease with the use of somatostatin analogues. The last PET-CT from July 2022 showed increased somatostatin receptor expression and decreased size (37 x 35 x 26 mm) compared to the previous one. So far, the patient has presented favorable evolution, without complications.

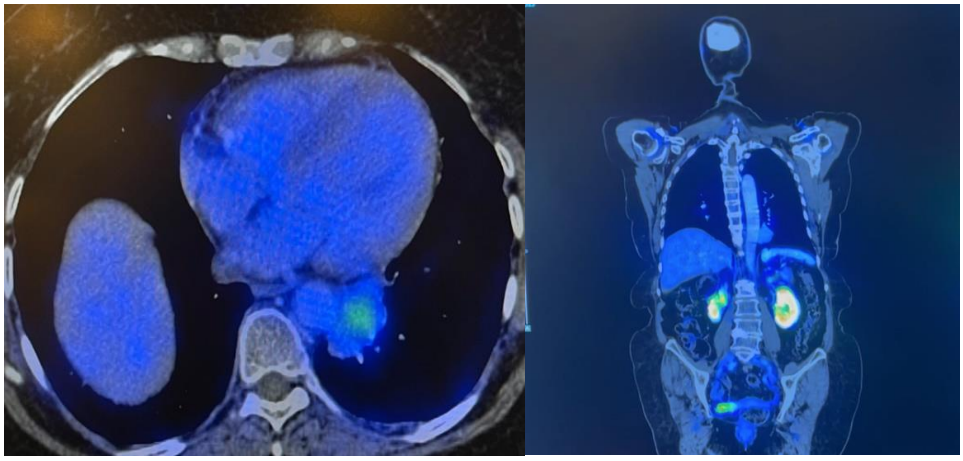

Figure 3: PET/CT Gallium 68 DOTA TOC 2022. A) Presence of left basal pulmonary spiculated lesion. B) Increased somatostatin receptors in tumor partially involving the abdominal aorta

DISCUSSION

Cyclic Cushing's syndrome, also called periodic or intermittent, is considered a very rare entity that is now more frequently recognized, which may be due to a higher index of suspicion and diagnostic tests [5]. In terms of etiology, both the adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent forms can cause cyclic Cushing's syndrome, more than 50% being caused by an ACTH-producing pituitary adenoma [6]. We present the case of cyclic Cushing's syndrome secondary to an ectopic ACTH-producing tumor, located at the left basal pulmonary level in a woman in her seventies, who presented a clinical picture characterized by intermittent weight gain, proximal myopathy, moderate hypokalemia, as well as uncontrolled hypertension; such symptomatology had irregular presentation intervals which made the diagnosis difficult. A large number of patients with cyclic Cushing's syndrome have very long periods of remission and therefore require long-term monitoring and follow-up. Some of the monitoring methods are: nocturnal salivary cortisol, 24-hour urine free cortisol, low-dose dexamethasone suppression test, hair cortisol concentration and dynamic tests [7].

Free cortisol in urine directly reflects the levels of biologically active cortisol in plasma and in comparison with the measurement of serum levels, it is not affected by diseases or drugs, having a sensitivity of 97% and specificity of 91%. On the other hand, nocturnal salivary cortisol is a non-invasive test that is not recommended for night shift workers, but it can be the method of choice because it is easy to repeat the sampling, as soon as the patient notices changes that suggest the resumption of signs or symptoms. Dynamic test represents the mainstay in the differential diagnosis of ACTH-dependent Cushing's syndrome, including the high-dose dexamethasone suppression test (HDST), CRH test and desmopressin test [1,8]. Treatment is etiologically focused and should be directed against the source of hypersecretion. Since the first line treatment for curative purposes is surgical resection of the lesion, our patient was evaluated by the thoracic surgery team, however, she rejected this therapeutic option due to the high surgical risk since the ACTH-producing tumor has contact with 25% of the aorta. In these cases in which tumor resection is life threatening or when surgery is not satisfactory, second line treatment such as steroid synthesis inhibitors (ketoconazole, metyrapone, etomidate), somatostatin analogues (octreotide, lanreotide) or dopaminergic agonists (cabergoline) is implemented [9].

Initially, our patient received treatment with ketoconazole at a dose of 200 mg every 8 hours and because the PET CT showed somatostatin receptor uptake, it was decided to complement treatment with octreotide 20 mg intramuscular every 4 weeks. Another therapeutic option in uncontrolled disease is radiotherapy [9] and ultimately bilateral adrenalectomy [10]. Finally, it has been observed that cyclic Cushing's syndrome has high recurrence rates (63%), but low remission (25%) compared to the classical form of Cushing's syndrome.

CONCLUSIONS

Cyclic Cushing's syndrome is a pathology that requires a high index of suspicion as the oscillating clinical picture and discrepant biochemical findings make diagnosis challenging. Individualized multidisciplinary treatment methods, long-term follow-up and timely treatment of complications may improve the prognosis of patients with cyclic Cushing's syndrome.

Source of Funding

This work did not receive any financial support.

Conflict of Interest

The authors declare that there are no conflicts of interest at the time of publication of this article.

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