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Prolonged Adrenal Insufficiency after Unilateral Adrenalectomy for Cortisolic Adenoma

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Abstract

Background: The suppression of the hypothalamic-pituitary-adrenal axis by cortisol-secreting adrenocortical tumors is well recognized and requires peri- and postoperative hydrocortisone substitution. **Case Presentation:** A 48-year-old female patient with hypertension and progressive weight gain, the clinical signs of hypercorticism motivated a hormonal workup revealing an independent ACTH Cushing's syndrome: with urinary free cortisol (UFC) at 649 nmol/24h (4× normal), adrenocorticotropin hormone (ACTH) at 1.5 ng/l. The rest of the hormonal workup was not performed due to a lack of financial means. An Adrenal CT scan showed a 4 cm right adrenal adenoma. The patient underwent a right adrenalectomy with an adrenal adenoma on pathological examination. The contralateral side was normal. The patient was treated with hydrocortisone 30 mg/d for 6 weeks then 15 mg/d, during the monitoring we noted a persistence of the adrenal insufficiency for now 4 years. Basal cortisol levels during follow-up were very low (<3 µg/dl) ruling out the need for synacthen stimulation tests. **Conclusion:** Adrenal cortisol tumors are recognized by suppression, the duration of hypothalamic-pituitary-adrenal axis suppression is variable from 11 to 60 months depending on the series, which depends on the duration, severity of hypercortisolism, tumor size and other unknown factors. A longer follow-up of these patients is necessary to look for recovery of the contralateral adrenal gland.

Keywords

Hypercorticism, Hypothalamic-Pituitary-Adrenal Axis, Adrenal Insufficiency

1. Background

Endogenous Cushing's syndrome (CS) is rare with an estimated incidence of 1 to 3 patients per million per year [1]. CS describes a group of diseases that have

in common an excess of glucocorticoid secretion responsible for a characteristic clinical phenotype. In 70% of cases, CS is secondary to an ACTH-secreting pituitary adenoma (Cushing's disease). In about 5% of cases, SC is caused by ectopic production of ACTH (ectopic CS), mainly by pulmonary neuroendocrine carcinoids. The third subtype is ACTH-independent SC, accounting for about 25% of cases, secondary to either a benign or malignant adrenal tumor or macro or micronodular adrenal hyperplasia.

The first-line treatment of CS is resection of the responsible tumor in all three subtypes. This surgery is invariably followed by tertiary adrenal insufficiency with the need for glucocorticoid replacement therapy [2].

The duration of this suppression is variable from 11 to 60 months depending on the series [3], it depends on the duration, the severity of hypercortisolism, the size of the tumor and other unknown factors [3].

We report a case of SC secondary to a cortisol adenoma in which the hypothalamic-pituitary-adrenal (HPA) axis is still slowed down. It is now 4 years postoperatively.

2. Case Report

The patient was 48 years old, with no particular pathological history, in particular no known diabetes, nor any notion of long-term corticosteroid therapy. The onset of the symptomatology dates back to about 2 years ago with the onset of excessive weight gain without any change in eating habits, asthenia, muscular fatigue, puffiness of the face, erythrosis of the cheekbones and appearance of purple stretch marks on the abdomen. This clinical picture was associated with arterial hypertension. The diagnosis of cushing's syndrome was made clinically in view of the presence of signs of hypercorticism such as facio-truncular obesity, overweight (BMI 28 kg/m^2), a puffy erythrosic face with filling of the supra-calvicular hollows, a buffalo hump, and purple stretch marks on the abdomen and the roots of the thighs (**Figure 1**).

The diagnosis of hypercortisolism was confirmed biologically by the determination of Urinary Free Cortisol (UFC) on 2 occasions: 649 nmol/24h rechecked at 634 nmol/24h: 3 times the normal value (30 - 200 nmol/l).

Due to a lack of resources, the rest of the biological work-up to be carried out in the presence of hypercortisolism was not done (1-mg overnight dexamethasone suppression, and late-night salivary cortisol level).

ACTH levels are measured to identify the subtype of CS and returned very low at 1.5 ng/l (normal values: 10.3 - 48.3 ng/l). The diagnosis of ACTH-independent CS was retained.

Adrenal CT showed a 4 cm right adrenal mass, well-defined, homogeneous, low density 8 UH (**Figure 2**) without an abnormality of the contralateral adrenal gland. the assessment of the effects of hypercorticism revealed a depressive syndrome, a well-controlled Blood Pression with irbesartan 150 mg/d, a normal fasting blood glucose level of 0.95 g/l, HbA1c of 5%, hypercholesterolemia,

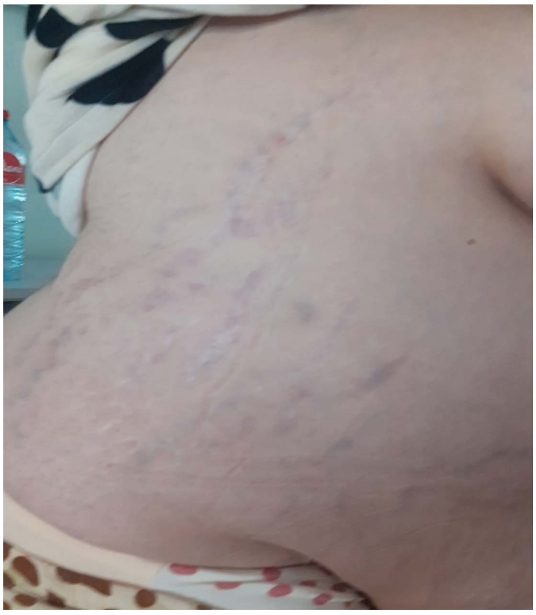

Figure 1. Thinned skin with wide purple striae.

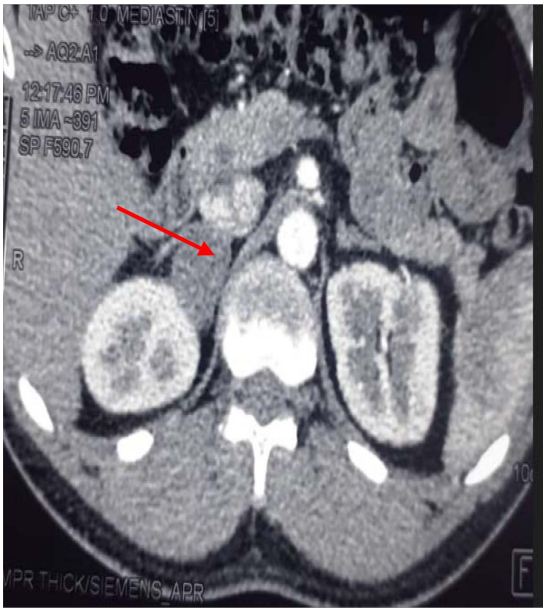

Figure 2. Well-defined right adrenal mass.

hypertriglyceridemia, a normal phosphocalcic and renal assessment transthoracic echocardiography was normal. An X-ray of the lumbar spine performed in the face of chronic low back pain revealed signs of significant spinal osteoporosis.

A right adrenalectomy was performed laparoscopically; surgical exploration of the left side revealed a normal adrenal gland. Macroscopic anatomopathological examination described an encapsulated and richly vascularized nodule. On microscopy, the tumor cells are in clusters, the cytoplasm is very granular, the nuclei are round or oval with prominent nucleoli without any aspect of necrosis or capsular infiltration or vascular invasion, this aspect is in favor of a benign

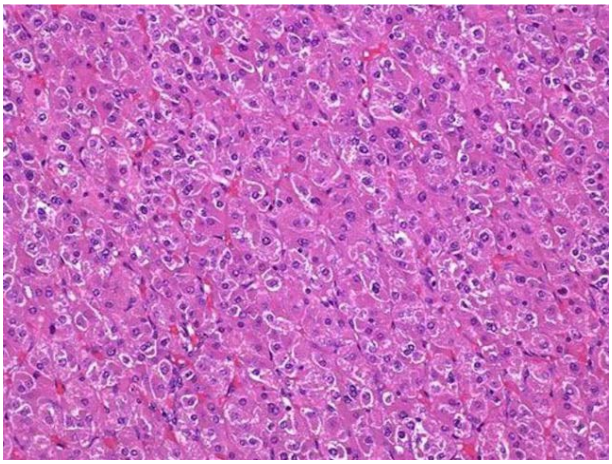

Figure 3. Adrenal adenoma with compact cells.

adrenal adenoma (**Figure 3**). The patient presented an acute adrenal insufficiency crisis postoperatively, she was put on hydrocortisone replacement 30 mg/d for 6 weeks then 20 mg/d. After the surgery we noted a regression of catabolic signs of hypercorticism, a loss of 8 kg over one year with persistence of the arterial hypertension.

3. Discussion

The suppression of the HPA axis by cortisol-secreting adrenal tumors is well recognized and requires peri- and postoperative hydrocortisone replacement [3].

Our case illustrates the lack of recovery of the HPA axis 4 years after unilateral adrenalectomy for adrenocortical adenoma responsible for severe hypercorticism that had evolved for more than 2 years.

The adrenal insufficiency is secondary to chronic exposure to an excess of glucocorticoids responsible for the inhibition of CRH-producing cells in the hypothalamus, the inhibition of the secretion of stored ACTH and the reduction of the transcription of the ACTH precursor gene POMC [4] [5].

In all studies published since 1981, the average prevalence of adrenal insufficiency after adrenalectomy is 99.7% (100% in all but one study, which reported a prevalence of 80%) [6].

The recommended dose of glucocorticoids as replacement therapy is 10 - 12 mg/m^2/day of hydrocortisone given two or three times daily [7]. The first dose should be given as soon as the patient wakes up. Other synthetic glucocorticoids may be given at the lower substitution dose when hydrocortisone is not available. This substitution should be tapered according to the clinical course and hormonal findings and should be maintained until recovery of the HPA axis.

The mean prevalence of HPA axis recovery in patients with ACTH-independent Cushing's syndrome reported in the major series published to date is 92%. Seven studies reported a total mean prevalence of 8% of patients who did not recover corticotropic function over a period of 69 to 103 months [6].

There is considerable heterogeneity between studies due to the lack of a stan-

dardized definition of HPA axis recovery after adrenalectomy. Most studies relied on clinical assessment and did not perform hormonal testing to define recovery.

A 250 µg synacthen test was used in only a quarter of the studies, with a normal 60-minute cortisol response threshold of 500 or 550 nmol/L or an 8-hour cortisol level > 165 nmol/L.

Recent recommendations suggest that the HPA axis should be assessed by measuring 8-hour cortisol every 3 months and performing a 250 µg synacthen test when the 8-hour cortisol level is >7.4 µg /dl. Recovery of the corticotropic axis is then defined by a baseline or post-stimulation cortisol > 18 µg /dl or 500 nmol/l [3].

The average time to recovery of normal HPA axis function after adrenalectomy for unilateral adrenal cortisol adenomas is 18 months (range 1 - 30 months in the major series published to date) [6] [7]. This time may range from several weeks to several years in other studies [5] and also depends on the initial severity of the cushing syndrome [8].

In a study comparing different subtypes of hypercortisolism, patients with adrenal Cushing's syndrome had the longest time to recovery of the HPA axis, followed by patients with Cushing's disease and those with ectopic Cushing's syndrome, with the latter showing the fastest return to equilibrium despite a similar dose of replacement glucocorticoids [9].

These data were also found by a study done by a German team in 2015 [2]. This retrospective study included 91 patients of the three subtypes of SC (Cushing's disease, ectopic CS, and adrenal CS) who underwent curative surgery and documented follow-up after excluding cases of persistent disease, pituitary irradiation, concurrent adrenostatic or somatostatin analogue therapy, and malignant adrenal disease.

This study showed that the probability of recovery of adrenal function in a 5-year follow-up differed significantly between the subtypes. It was 82% in ectopic SC, 58% in CD, and 38% in adrenal SC. The median time to recovery also differed between subtypes: 0.6 years (interquartile range [IQR], 0.03 - 1.1 years) in ectopic CS, 1.4 years (IQR, 0.9 - 3.4 years) in CD, and 2.5 years (IQR, 1.6 - 5.4 years) in adrenal CS.

A study by Hee Kyung Kim *et al.* [10] in patients with subclinical cushing's syndrome compared with those with established SC showed that the time to recovery of the HPA axis after adrenalectomy in patients with SCIC is rapid and depends on the degree of cortisol excess, hence the need for a more precise definition of SCIC for better patient management and to avoid the risk of under- or over-treatment of patients.

Recovery of HPA axis function follows a stepwise process involving the hypothalamus and pituitary gland in the early post-surgical period and then the adrenal cells in a second phase. The phases of recovery of adrenal function in patients undergoing adrenalectomy for Cushing's syndrome due to unilateral adenomas can be summarized as an early phase of hypothalamic and adrenal

insufficiency, followed by recovery of ACTH secretion to above normal levels and subsequent restoration of normal glucocorticoid secretion [6].

This specific pattern of recovery appears to be independent of the cause of hypercortisolism and has also been observed in patients with iatrogenic Cushing's syndrome after stopping corticosteroid therapy.

Despite proper hydrocortisone replacement many patients may show signs of adrenal insufficiency essentially anorexia, nausea, weight loss, fatigue, myalgias and psychiatric disorders [11] [12].

These symptoms may improve after a temporary increase in the dose of replacement therapy.

However, there is no evidence that supra-physiological doses of glucocorticoids in the early postoperative period could limit the development of glucocorticoid withdrawal syndrome [13].

4. Conclusions

After successful treatment of Cushing's syndrome (CS), secondary adrenal insufficiency develops as a result of prior suppression of the HPA axis by excess cortisol in the body. Pending recovery of the axis, glucocorticoid replacement is necessary to allow normal body function and prevent an acute adrenal crisis.

The median time to recovery of the HPA axis is variable in various cohorts of CS patients ranging from several weeks to several years. Despite glucocorticoid replacement after recovery from HC, patients often present with symptoms of glucocorticoid withdrawal syndrome.

It is imperative to educate patients on the expectations of HPA axis recovery and to ensure the management of the signs of glucocorticoid withdrawal syndrome based on individual preoperative parameters.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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