

## A Long-Standing Subtle Cushing's Syndrome Induced by a Unilateral Macronodular Adrenal Hyperplasia

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### Abstract

Cushing's syndrome is a clinical picture characterized by signs and symptoms associated with a prolonged exposure to inappropriately high level of the hormone cortisol. Described for the first time by Harvey Cushing in 1932, iatrogenic cause, by taking drugs, is the common condition nowadays. The most common non-iatrogenic cause of Cushing's syndrome is Cushing's disease, referring to a tumor (generally adenoma) in the pituitary gland produce large amounts of ACTH, causing the adrenal glands to produce elevated levels of cortisol. Less frequent is Cushing's syndrome due to primary adrenal disease. The typical features of the Cushing's syndrome usually allows an easy diagnosis but many times the clinical picture is much less clear. The current manuscript reports the history of a woman affected by a very long and overlooked history of hypercortisolism, approximately 10 years. Through the years it was not possible to confirm adrenal hyperfunction and the patient was treated considering very common symptoms (obesity, hypertension, osteoporosis). Functional tests and CT imaging finally showed a primitive functional nodule of the adrenal gland. Laparoscopic adrenalectomy lead to complete regression of the hormonal excess, with disappearance of classical Cushing's clinical features. Histology was consistent with a macronodular hyperplasia showing two well capsulated lesions with respect to the surrounding adrenal tissue.

**Keywords:** Cushing's syndrome; Unilateral macronodular adrenal hyperplasia; Adrenalectomy

### Introduction

In its overt expression Cushing's syndrome is usually easily recognized but more subtle forms can represent a significant challenge for physicians, frequently missed in the diagnostic workup [1]: in a small case series of a single centre the mean time to diagnosis after the appearance of the first symptoms of Cushing's syndrome was 6.0 years in spite of several medical evaluations [2]. The often slow progression of the clinical picture with the presence of non-specific symptoms, frequently encountered in common conditions such as obesity, hypertension, and diabetes mellitus may deceive the physician and delay the correct diagnosis. To confirm these difficulties the term subclinical Cushing's syndrome was proposed to describe an autonomous cortisol hypersecretion which is not sufficient to generate the overt syndrome [3]; in addition a particular form of cyclical cortisol hypersecretion, with periods of clinical and biochemical remission, was described [4]. Here we present a clinical case of a woman repeatedly evaluated for common medical problems in a range of time of approximately 10 years without the beginning of an extensive and appropriate diagnostic approach for Cushing's syndrome: at last this happened with the demonstration of a unilateral macronodular adrenal hyperplasia, successfully removed with consequent significant clinical improvement.

### Case Presentation

A 69-yr-old Caucasian woman was referred to our unit for inadequate blood pressure control and detection of low potassium

levels in routine blood tests. She was overweight (height 153 cm, weight 65 kg, BMI=27), non-smoker, and suffered diffuse mild joint pain with osteoarthritis and osteoporosis. In the past she had undergone investigations for suspected lupus erythematosus, without diagnostic confirmation, and psoriasis. She presented central obesity, an initial *facies lunaris* (Figures 1 and 2) and high blood pressure despite the administration of four drugs (valsartan, clonidine, nebivolol and a thiazide diuretic). This clinical condition lasted for more than 10 years and, despite the presence of central obesity and hypertension, the lack of purple striae and the normal glycemic control, together with negative basal hormonal tests and initial imaging studies performed, did not corroborate the suspected diagnosis of Cushing's syndrome [5]. At the admission in our unit blood tests showed hypokalaemia (2.3 mEq/L), cortisol levels = 5 µg/dL at 8.00 am and 4.3 µg/dL at 6.00 pm; aldosterone, renin, and the other routine tests were normal (except for high cholesterol and triglyceride levels); free urinary cortisol excretion was 190 µg/24 h. Free urinary cortisol level superior than 145 µg/24 h are indicative of Cushing's syndrome [5]. After the administration of potassium IV to correct blood levels and the withdrawal of both the diuretic and the β-blocker, the patient was reassessed in terms of adrenal secretion. Basal cortisol serum levels were 5.3 µg/dL at 8.00 am and free urinary cortisol excretion was 200 µg/24 h; ACTH basal levels at 8.00 am were 6.4 ng/L. After 1 mg dexamethasone oral administration at 11 pm fasting serum cortisol levels at the following day were 8.1 µg/dL; after a standard low-dose dexamethasone suppression test (0.5 mg every 6 h for 48 h) urinary cortisol levels remained 161 µg/24 h, not suppressed. The effects of both ACTH (1 µg iv) and ovine CRH (1 µg/kg iv) administration on cortisol serum levels are shown in fig. 2: after ACTH administration cortisol levels started at 6.6 µg/dL and peaked at 39.1 µg/dL, whereas 17-OH-progesterone started at 0.02 µg/L and

peaked at 2.47  $\mu\text{g/L}$  (data not shown); after ovine CRH administration both cortisol and ACTH serum levels did not change significantly (from 9.2  $\mu\text{g/dL}$  to 9.3  $\mu\text{g/dL}$  and from 6.8 ng/L to 7.1 ng/L, respectively). Low levels of ACTH suggest Cushing's syndrome can be caused by a tumor in the adrenal glands or another area of the body [6]. Moreover cortisol and ACTH level after ovine CRH administration did not differ significantly, and this result does not confirm the presence of a pituitary tumor. The urinary excretion of catecholamines and their metabolites was normal. The hormone results suggested an adrenal origin of the Cushing's syndrome and CT scan confirmed the presence of a 30x25 mm nodule of the right adrenal gland (Figure 3). Therefore the patient was submitted to laparoscopic right adrenalectomy and the histology was consistent with a macronodular hyperplasia showing two well capsulated lesions with respect to the surrounding adrenal tissue (Figure 4). Surgical adrenal gland resection is a typical indication of minimally invasive surgery, and also in our case, the patient was placed in left lateral decubitus using four entrances in a classical laparoscopic approach, with continuously invasive hemodynamic surveillance. 3 months after surgery the patient demonstrated adequate blood pressure control with a low-dose angiotensin II receptor antagonist, a decrease in body weight (BMI=23) and disappearance of *facies lunaris* (Figure 5); perioperative steroid replacement was necessary to avoid adrenal insufficiency but after 6 months, in absence of any replacement therapy, urinary cortisol excretion and serum potassium levels were normal. Basal plasma cortisol levels were 5.7  $\mu\text{g/dL}$  and ACTH administration (1  $\mu\text{g IV}$ ) induced an increase with a peak at 15,6  $\mu\text{g/dL}$ .

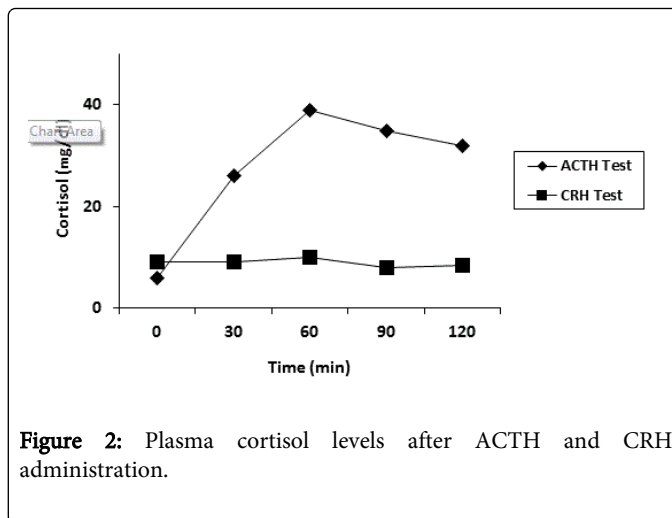


Figure 2: Plasma cortisol levels after ACTH and CRH administration.

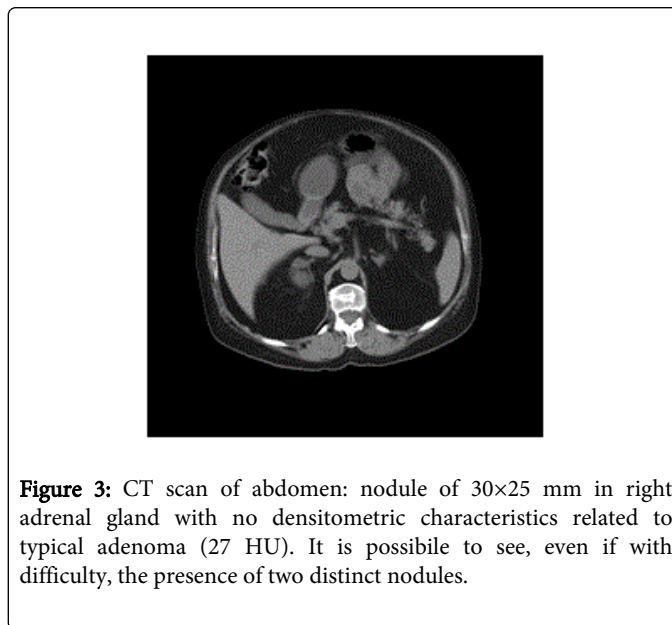


Figure 3: CT scan of abdomen: nodule of 30x25 mm in right adrenal gland with no densitometric characteristics related to typical adenoma (27 HU). It is possible to see, even if with difficulty, the presence of two distinct nodules.

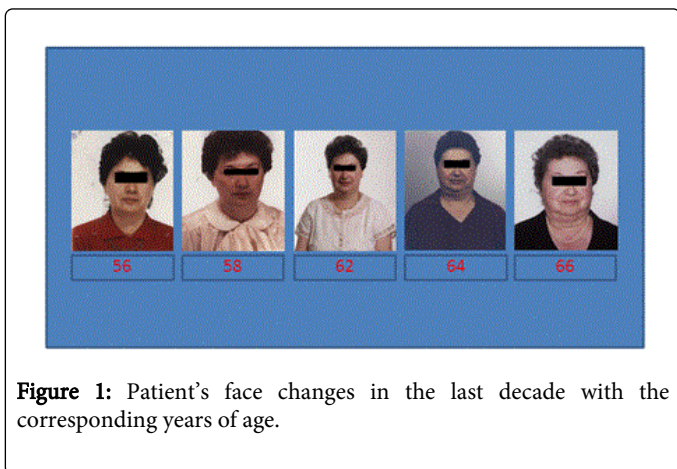
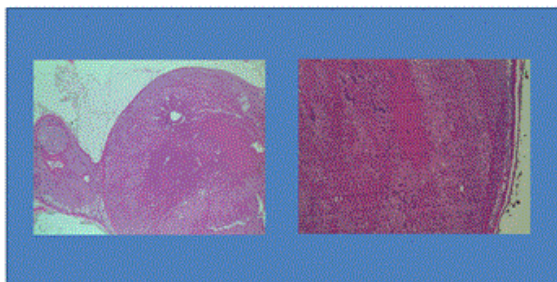


Figure 1: Patient's face changes in the last decade with the corresponding years of age.



**Figure 4:** Histology of the right adrenal gland: macronodular hyperplasia showing 2 well capsulated nodules (4x, hematoxylin-eosin). On the right an enlargement with clear cytoplasm cells, microvesicles, arranged in cords and trabeculae (10x, hematoxylin-eosin).



**Figure 5:** The patient at a follow-up visit 6 months after right adrenalectomy: in addition to good blood pressure control, normal values of potassium and normalization of hormonal tests the patient presents a decrease in weight (BMI=23) and disappearance of facies lunaris.

## Discussion

Cushing's syndrome is an uncommon condition with an incidence rate between 1.8 and 2.4 patients/million per year [7]. The patient presented a very subtle form of Cushing's syndrome: the previous physicians who had her in charge focussed on the very common symptoms (obesity, hypertension, osteoporosis) but they did not look at a confirmation of adrenal hyperfunction (collecting the clinical history we found a written evaluation of an experienced academic physician who 10 years ago denied the possibility to demonstrate this diagnosis). Recently many reports presented clinical series of patients who demonstrated an autonomous cortisol hypersecretion without an

overt Cushing's syndrome but with some clinical problems such as insulin resistance or type 2 diabetes, obesity, dyslipidaemia, hypertension, and marked osteoporosis: the term subclinical Cushing's syndrome was proposed [3,7-11]. In our case a mild form of *facies lunaris* was present and induced us to perform adequate hormonal tests and confirmatory imaging. Another possibility to explain the difficulty in diagnosing the Cushing's syndrome could be the occurrence of a cyclic cortisol hypersecretion, with repeated episodes of cortisol excess interspersed by periods of normal secretion [4,12]: obviously we had no hormonal data to confirm this hypothesis. The cortisol hypersecretion in our case was determined by a unilateral macronodular adrenal hyperplasia with the histological demonstration of two well capsulated nodules: at our knowledge this is an unusual presentation and we found only a previous observation in the literature [13]. We did not perform adrenal vein sampling to confirm the lateralization of the cortisol secretion but the clinical course after the right adrenalectomy confirmed our diagnostic conclusions.

## Conclusion

This report suggests the necessity to perform some simple screening tests for autonomous adrenal hypersecretion (such as the determination of the urinary cortisol excretion) in order to avoid to miss the diagnosis of Cushing's syndrome in subjects presenting very common clinical features such as hypertension and obesity; the full expression of the syndrome can necessitate many years and an early diagnosis can prevent important complications. The radiologic features of adrenal mass are helpful in making the diagnosis, but they cannot distinguish between functional and not functional lesions. Dynamic tests should always perform to correctly distinguish the many disease that can occur with Cushing's syndrome [14,15].

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