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

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 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 39.1 μg/dL, whereas 17-OH-progesterone started at 0.02 μg/L and peaked at 39.1 μg/dL.
peaked at 2.47 μg/L (data not shown); after ovine CRH administration both cortisol and ACTH serum levels did not change significantly (from 9.2 μg/dL to 9.3 μg/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 30×25 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 µg/dL and ACTH administration (1 μg IV) induced an increase with a peak at 15.6 µg/dL.

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

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

Figure 3: CT scan of abdomen: nodule of 30×25 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.
diagnosis). Recently many reports presented clinical series of patients

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 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].

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].

References

11. Di Dalmazi G, Vicennati V, Rinaldi E, Morselli-Labate AM, Giampalma E, et al. (2012) Progressively increased patterns of subclinical cortisol hypersecretion in adrenal incidentalomas differently predict major 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.

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.


