Clinical Cases

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Adrenal and Pituitary Incidentalomas in a Case of Cushing's Syndrome

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Rezumat

Incidentaloame adrenale și hipofizare într-un caz de sindrom Cushing

Sindromul Cushing este una dintre patologiile endocrine în care chirurgia poate salva vieți. Diagnosticul corect depinde de paternul hormonal bazal al pacientului, corelat cu diferite teste dinamice și investigații imagistice. Prezentăm cazul unei paciente cu sindrom Cushing, asociat cu tumori adrenale bilaterale și un microadenom pituitar. Pacienta prezenta nivele crescute de cortizol plasmatic, nesupresibile în timpul testelor cu doză mică şi cu doză mare de dexametazonă. S-a practicat adrenalectomie laparoscopică dreaptă, după care pacienta a dezvoltat insuficiență suprarenală acută. La 2 ani de la intervenție, încă necesită terapie de substituție suprarenală. Insuficiența suprarenală acută este o complicație severă a chirurgiei adrenale, cu o mortalitate înaltă dacă nu este recunoscută.

Cuvinte cheie: sindrom Cushing, adrenalectomie, incidentaloame

Abstract

Cushing's syndrome is a pathological condition where surgery may be lifesaving. The proper diagnosis depends upon the hormonal pattern of the patient, various dynamic tests and imagistic investigations. We report a case of a patient with Cushing's syndrome, with bilateral adrenal tumors and a pituitary microadenoma. She presented increased levels of basal cortisol, unsuppressed during a low and a high dose Dexamethasone test. She underwent right laparoscopic adrenalectomy and developed acute adrenal insufficiency. Two years after the intervention, she still requires adrenal substitution therapy. Acute adrenal crisis is a serious complication of adrenal surgery, with high mortality if unrecognized.

Key words: Cushing's syndrome, adrenalectomy, incidentaloma

Introduction

Cushing's syndrome represents a severe condition, consisting in exogenous or endogenous excess of corticosteroids. While iatrogenic cases are the most frequent, the endogenous hyper secretion has an incidence of 2-3 cases per 1,000,000 people per year (1). There are ACTH dependent causes as pituitary adenoma or paraneoplasic syndromes, (representing up to 80 % of all endogenous cases in adults) and ACTH-independent conditions (2). These include adrenal adenomas or carcinomas, and ACTH-independent bilateral adrenal hyperplasia.

Despite recent progress in the diagnosis and therapeutically management of Cushing's syndrome, it is still laden with high mortality and morbidity, mostly because of cardiovascular and

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metabolic complications, like hypertension, diabetes mellitus, dyslipidemia and obesity (1).

Case report

37 years old female patient was admitted for progressive weight increase (almost 15 kg), associated with the development of red-violet striae for the last 3 years. The medical history revealed severe hypertension (up to 200/100 mmHg) partially controlled by medication for the last 2 years. Recently she was diagnosed with diabetes mellitus and started on oral medication (Metformin).

The clinical exam showed: obesity (body mass index - BMI of 31.25 kg/m^2), with central pattern, round face, with red abdominal, axillary and mammary striae, mild hirsute pattern, capillary fragility, insomnia and depressive mood. The blood pressure was 200/120 mm Hg.

The biochemical parameters revealed: mild leukocytosis with neutrophilia (white blood cells – 11.300/mm^3, neutrophiles - 77.4%, with normal range between 4.000 - and 9.000, respectively 43-70%), dyslipidemia (cholesterol – 373 mg/dL, normal values <200 mg/dL, triglycerides – 651 mg/dL, normal values < 150 mg/dL) and hyperglycemia (138 mg/dL, normal range below 110 mg/dL).

The endocrine profile showed increased basal plasma cortisol and urinary metabolites, as well as lack of inhibition at Dexamethasone (DXM) suppression test that suggested a Cushing's syndrome (Table 1). Because of the obesity and depression, thyroid hormones were measured but they were within normal parameters. The hypertension could have been caused by a pheocromocytoma but the plasma metanephrines were normal (metanephrines – 15 pg/mL, normal range between 10 and 45 pg/mL, normetanephrines – 51 pg/mL, normal range between 15 and 90 pg/mL). In order to evaluate the etiology of endogenous hypercorticism, imagistic tests were performed. The abdominal computed tomography (CT) showed bilaterally adrenal hyperplasia but also a right adrenal tumor of 3.2 by 2.4 cm, that was well defined, with negative spontaneous density and low iodine uptake. In the left adrenal gland there was a smaller nodule of 1.2 by 0.85 cm, with similar characteristics (Fig. 1). The pituitary CT scan revealed a microadenoma of 0.7 by 0.3 cm. (Fig. 2)

Table 1. *Plasmatic cortisol and urinary metabolites*

	Bazal	DXM 2mg*2d	DXM 8mg*2d	Normal range
Plasmatic cortisol (microg/dl)	30.83		30.96	4.6-22.4
Free urinary cortisol (microg/24 h)		390.92		< 100
17OHCS (mg/24 h)	18.37	17.56	8.96	3.5-5.5
Urinary creatinine (g/24 h)	1.84	0.72	0.8	1.5-2



Figure 1. *Right adrenal tumor of 3.2 by 2.4 cm, and a left adrenal gland nodule of 1.2 by 0.85 cm*

Based on these, Cushing's disease was suspected and for the beginning right laparoscopic adrenalectomy was performed – the patient having refused pituitary surgery. There were no incidents during the procedure. The pathology exam showed benign aspects. Four days after the intervention, the patient developed general malaise associated with hypotension, diffuse abdominal pains, fever, and nausea with vomiting. She had persistent leukocytosis with neutrophilia (WBC – 13,000/mmc; neutrophiles – 77 %), hepatic cytolysis (AST – 64 U/L, normal range < 34 U/L; ALT – 125 U/L,

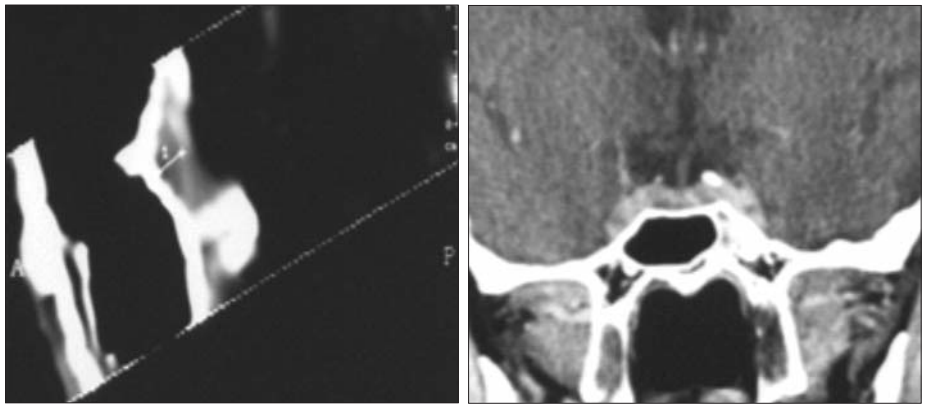


Figure 2. *Pituitary CT scan: microadenoma of 0.7 by 0.3 cm*

normal range < 31 U/L). The abdominal CT showed only a small quantity of liquid around the liver, with thickened diaphragmatic pleura. (Fig. 3) A reevaluation of the initial hormonal results showed a suppressed ACTH value (8.08 pg/mL, normal range between 10 and 60 pg/mL), which was not available at first. At the moment, extremely low levels of plasma cortisol -2.27 were found (normal between 11 and 22 μg/dL) and low level of ACTH, too - 3.1 pg/mL). These suggested that the Cushing's syndrome was actually ACTH independent, probably caused by one of the two bilateral adrenal tumors. In fact, the adrenal adenoma secreting cortisol was the one removed and the patient developed acute adrenal failure due to the inhibition of the hypothalamic – pituitary – adrenal axis by this tumor. This was a life threatening condition and emergency therapy with hydrocortisone i.v., 200 mg per day was started together with hydro-electrolytic solutions. The patient's condition improved rapidly, thus 10 days later she was discharged with substitution therapy: oral Prednisone, 5 mg per day, associated with oral anti-diabetes medication Metformin 1000 mg per day and lipid lowering therapy. No hypotensor drug was necessary.

6 month after the surgery, she had partially lost the excess weight (BMI – 27.7 kg/m^2); the abdominal striae had become pale. The "moon face" disappeared. (Fig. 4) The blood pressure rose again (maximum 170/100 mm Hg) and the anti-hypertensive medication was resumed. The low levels of cortisol persisted (4.55 μg/dL) as well as ACTH (1.357 pg/mL). The patient did not tolerate the withdrawal of the Prednisone, developing malaise and abdominal pains. The adrenal insufficiency was still presented and the arterial hypertension was probable essential. The pituitary microadenoma was stationary, as well as the left adrenal nodule, that are both incidentalomas. (Fig. 5, Fig. 6) The substitution therapy with Prednisone was continued for 2 more years.

Discussions

The majority of ACTH independent Cushing's syndrome is determined by adrenal adenomas and rarely by adrenal carcinomas or ACTH-independent macro nodular adrenal hyperplasia or primary pigmented nodular adrenal disease. To our knowledge, there are rare the cases of Cushing's syndrome determined by an adrenal hyper functioning adenoma that coexists with a non-secretory adenoma on the other adrenal gland (3,4). For example, two cases were described in Japan, with right location, too. In both cases, after the removal of the secreting tumor, the patients did not present the relapse of Cushing's syndrome. In such cases, bilateral adrenal venous sampling with cortisol profile may help to differentiate between the secretory and the non-secretory tumor (5). In our case, the differential diagnosis was difficult because the presence of pituitary adenoma that mimics Cushing's disease. After the adrenalectomy, the acute adrenal failure was revelatory for the correct etiological diagnosis of the Cushing's syndrome and the proper diagnosis was life saving. In case of unilateral adrenalectomy for Cushing's disease, the adrenal insufficiency is not registered but sometimes the clinical features may not progress.

Cushing's syndrome represents between 7.1 and 24% of all the diagnosis for whom laparoscopic adrenalectomy is performed (6-9). The laparoscopic procedure is preferred in adrenal tumors because of reduced risk of intra and postoperative complications, lower hospital stay and faster recuperation. Even large tumors can be removed by this technique (10,11). In a retrospective study in the Danes that underwent laparoscopic adrenalectomy the conversion rate was 7.6% and mortality was 1%. The complication rate forminimal invasive surgery was 16% compared with 25% for open adrenalectomy, but other studies report a lower rate of 6% (6,12).



Figure 3. *Postoperatory abdominal CT scan: a small quantity of liquid around the liver, and thickened diaphragmatic pleura*



Figure 4. *Normal face features, persistent hirsutism*

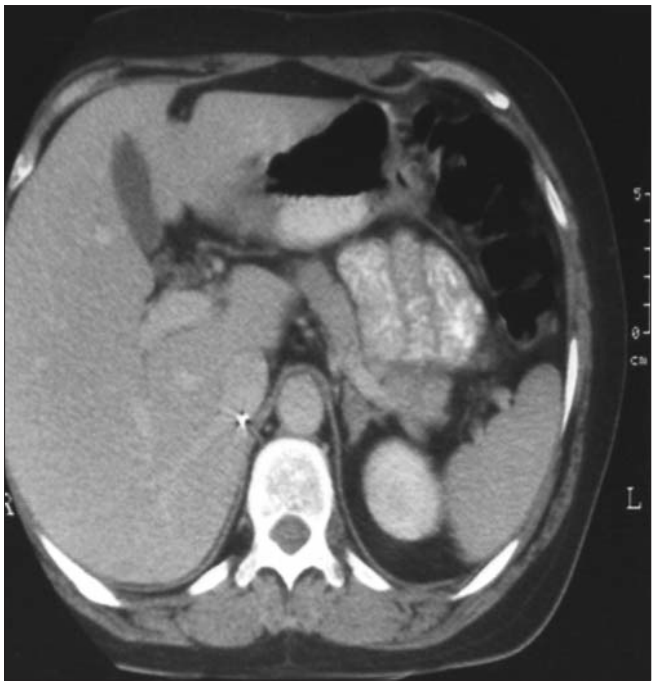


Figure 5. *Abdominal CT scan: stationary left adrenal nodule*

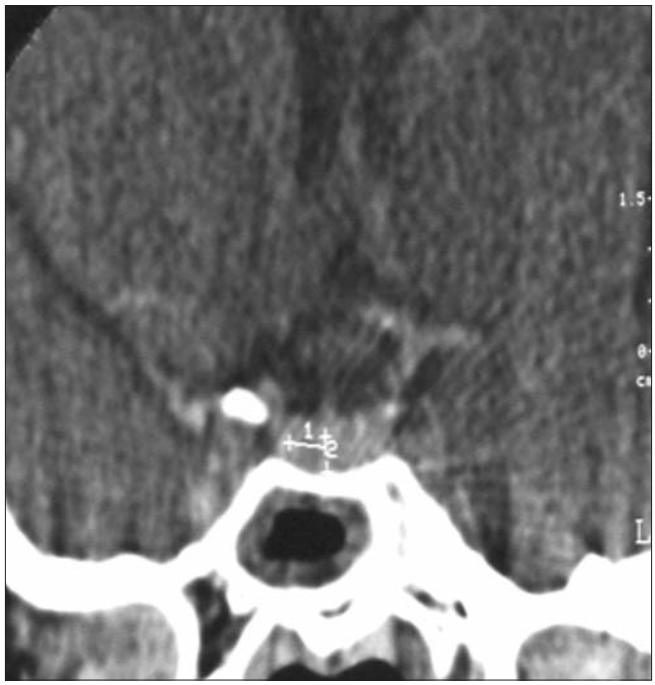


Figure 6. *Cerebral CT scan: stationary pituitary microadenoma*

The procent of intraoperatory complications is similar regardless of the benign pathology of the patient (13) but the postoperatory complications are more frequent in patients receiving corticoids, especially infections (14)

Patients who undergo bilateral adrenalectomy or unilateral adrenalectomy for Cushing's syndrome require substitution therapy immediately after the surgery. Despite that, up to 7% develop acute adrenal failure (14). Adrenal insufficiency can go unrecognized in such critically ill patients, so the medical team must bear it in mind. It can appear even in cases with sub-clinical Cushing's and some authors recommend screening for adrenal crisis by measuring basal plasma cortisol in the first day after surgery in all patients with incidentalomas (15). Considering that up to 20% of adrenal incidentalomas secrete cortisol independent of ACTH, acute adrenal insufficiency has to be considered in all patients who underwent adrenal surgery and develop suggestive symptoms (14,16). These include hypotension, anorexia, weakness, fatigue, lethargy, fever, and even confusion or coma. The diagnosis may be delayed by the digestive symptoms, like nausea, vomiting, abdominal pain which can mimic acute abdomen. Unnecessary abdominal intervention can lead to increased mortality. Parenteral substitution therapy has to be started immediately.

The recovery from adrenal failure depends on patient; usually it is temporary. In majority of cases is registered for 2 years. But this represents a life threatening condition (17). In a study, 32 patients who underwent unilateral adrenalectomy for Cushing's syndrome needed substitution therapy for up to 8 years, on average 30 months (18). Other authors describe a shorter period of recovery of up to 9 month (19). Our patient needed therapy for over 2 years.

On the other hand, the initial symptoms of Cushing's syndrome persist variably. In one study, 60 patients who underwent adrenalectomy for Cushing's syndrome had signs of cortisol excess for 7-9 month after surgery, but in some persisted over 4 years (18). The most optimistic research shows that about two thirds of the patients normalized their blood pressure and weight after the adrenalectomy (20). But other studies show a less favorable result, with high percentage of patients presenting persistent obesity (41%), hypertension (31%), proximal muscle weakness (44%) and insulin-dependent diabetes (29%), after a mean follow up of 60 months (19). This is also the case of our patient, in which hypertension and diabetes persisted but an essential component as seen in metabolic syndrome may be involved.

The long-term implications of a patient who suffered adrenalectomy for Cushing's syndrome suggested, according to older studies, a similar mortality for cured patients when compared with the general population (21,22). However, cardiovascular pathology seems to be increased in patients with persistent hypercorticism, with a standard mortality ratio increased by 3.8 up to 5.0 compared with the general population (1). According to a Danish study performed on 166 patients diagnosed with different types of Cushing's syndrome mortality in patients with removed adrenal adenomas was 4 times higher than the general population, especially in the first year post surgery (23). Even in cured patients, the cardiovascular risk factors like abdominal obesity and insulin resistance persist after surgery, implying a raise in mortality (24). Beside alteration in insulin sensibility and lipid profile, others biochemical disturbances appear like endothelial lesions, inflammatory markers, immuno-modulators, most of them being related rather to

the obesity and hypertension than the hypercortisolism itself. For example, the levels of osteoprotegerin and interleukin – 8 decreased to normal after the surgical cure of Cushing's syndrome while C-reactive protein (CRP) and soluble intracellular adhesion molecule 1 (sICAM) increased to normal. CD40 ligand, considered a marker for platelet-mediated inflammation increased above normal after surgery (25). Endothelin 1, a powerful vaso-constrictor, is 3 times higher in patients with Cushing's syndrome, but unrelated with the levels of plasma cortisol. Its levels decrease after surgery (26). Health related quality of life also seems affected in patients with Cushing's syndrome, despite an initial improvement after adrenal or pituitary surgery (27).

The non-functioning pituitary adenomas may be discovered by the mass effect, including hypopituitarism. This is the case of tumors having more than 1 cm diameter. The accidentally discovered microadenomas have no effects and no risk of growing (28). The management of pituitary incidentalomas consists mainly in follow up by serial imagistic scan. Some call it the "watch and wait" policy. The prevalence is 70-90 cases/million population and they comprise 7-14% of all pituitary diseases (29). To our experience, once the diagnosis of non-secretory tumor is established, the CT scan should be performed no soon that 24 months (30). Other authors recommend as management the first IRM scan after 6 months from the initial diagnosis, than yearly for 5 years, and later every 2 or 3 years (31).

Regarding adrenal incidentalomas there is a more complex situation based on the fact that even most of them are non-functional benign tumors; the surgical re- movement may become an option (32). They are discovered even if they are clinically inapparently for reasons other than the evaluation of the adrenal gland. This was not our case, the investigation of pituitary-adrenal axes was actually the reason of the diagnosis (33). The adrenal incidentalomas represent a continuing management dilemma that is still a matter of debate (34).

Conclusions

Laparoscopic adrenalectomy is the gold method of treatment for adrenal tumors. After surgery, adrenal insufficiency complicates the post-operator evolution. It must be recognized and treated in time because it carries a high mortality load. In our case, the diagnosis was more difficult due to the collateral presence of another adrenal tumor, that turned out to be an incidentaloma and also because of the pituitary incidentaloma, mimicking Cushing's disease.

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