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CASE REPORT

Lung Carcinoid Tumors and Paraneoplastic Cushing's Syndrome: Diagnostic and Therapeutic Difficulties - A Case Report

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ABSTRACT

Introduction. - Paraneoplastic Cushing's syndrome is a rare cause of endogenous hypercorticism. It is caused by an ectopic secretion of adenocorticotropin (ACTH) by a non-pituitary endocrine tumor. The biological and radiological data cannot specify the etiology of this syndrome, which creates a problem of differential diagnosis with Cushing's disease. In addition, these tumors are often too small to be localized and their location is extremely variable. As a result, the difficulties of localization require the use of specific imaging techniques.

Case Report. - We report the observation of a 44-year-old man with a medical history of diabetes and high blood pressure, presenting with a severe and rapidly progressive Cushing syndrome, due to a hypercorticism caused by an ectopic ACTH secretion. The lung computed tomography performed to search a neoplastic origin found a 15 mm nodule in the middle lobe. Indium-111-labeled octreotide scintigraphy found significant uptake in the lung nodule.

The middle lobe was resected. The postoperative recovery was uneventful. Postoperative pathology confirmed the presence of a typical carcinoid tumor, and the immunohistochemical complement showed tumor cell positivity for ACTH, CD56, chromogranin and synaptophysin.

Conclusion. - This observation illustrates the dilemma between the need to locate an ectopic ACTH secretion and the control of aggressive and threatening Cushing's syndrome. An early use of the octreotide scintigraphy should be considered if a topographic diagnosis of the causative tumor cannot be done through the conventional imaging techniques.

Key words: Paraneoplastic Cushing's Syndrome, Positron Emission Tomography, Classical Carcinoid Tumor.

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INTRODUCTION

Paraneoplastic Cushing's syndrome represents 10 to 17% of adenocorticotropin (ACTH) dependent Cushing syndrome cases. It induces, in its classical form, a major and rapidly evolving hypercorticism (1,2). This ectopic secretion is secondary to neuroendocrine tumors with variable size and location, but the most frequent are lung carcinoid tumors (1). As these tumors are often small and their location is difficult to determine, they constitute a real challenge for clinicians. Few studies reported cases of paraneoplastic Cushing's syndrome, what motivated us to report the case of a patient presenting with a severe and rapidly progressive Cushing's syndrome caused by a typical lung carcinoid tumor.

CASE REPORT

A 44-year-old man, heavy smoker (50 pack-years), with a medical history of type 1 diabetes since 2003 with degenerative complications and arterial hypertension since 2013, visited the endocrinology department in September

2014, with Cushing's syndrome symptoms associating facial erythrosis, central obesity involving the trunk and face (moon face) with sparing of limbs and purple striae (figure1). No bronchial nor carcinoid symptom was noted. Laboratory test results revealed an elevated serum cortisol level, and no response to either low- nor high-dose dexamethasone suppression.

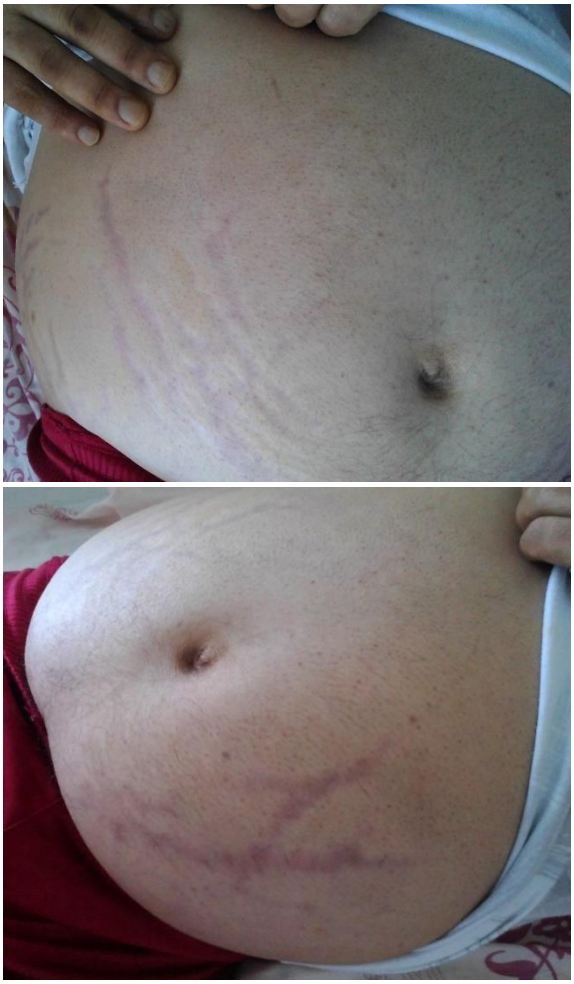

Figure 1: Abdominal purple striae

The pituitary magnetic resonance imaging (MRI) revealed no abnormalities in the pituitary gland. Abdominal computed tomography (CT) scan revealed a bilateral adrenal hyperplasia (figure2). Thoracic CT scan (figure 3) showed a pulmonary nodule of the middle lobe measuring 15 mm. Indium-111-labeled octreotide scintigraphy (figure 4) found significant uptake in the lung nodule.

The assessment of complications noted hypertension well controlled under quadruple anti-hypertensive therapy, diabetes evolving for 11 years, insulin-requiring, unbalanced with an HbA1c at 10%, diabetic retinopathy, diabetic nephropathy, hypokalaemia at 3 mmol / L, dyslipidemia with LDL cholesterol at 1.65 g / L, and triglycerides at 3.87 g / L despite taking statins. Bone densitometry revealed osteopenia. The liver ultrasound showed a fatty liver.

The patient was treated with ketoconazole (800 then 1200 mg /day), which was well tolerated clinically and biologically.

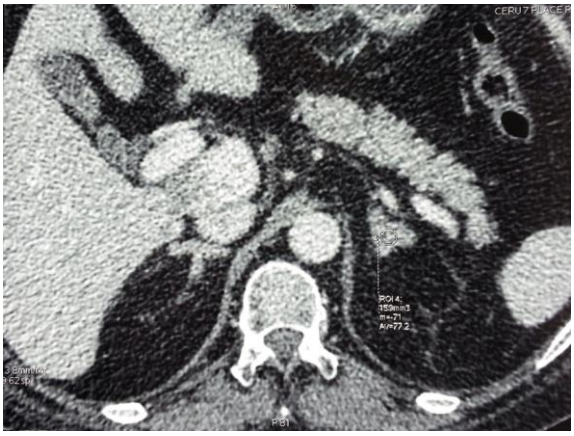

Figure 2: Abdominal computed tomography scan : bilateral adrenal hyperplasia.

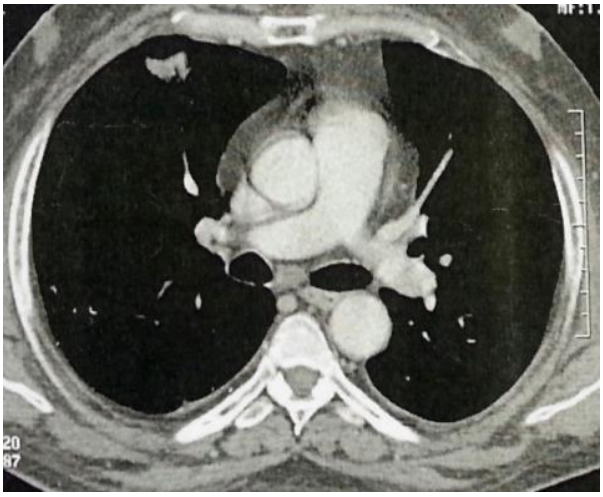

Figure 3: Thoracic CT scan : pulmonary nodule on the middle lobe.

Clinical course exhibited no changes in Cushing's syndrome symptoms, with consistently elevated cortisol levels and the onset of mental disorders such as agitation and persecutory delusions.

The patient was hospitalized into a psychiatric department and an organic cause of these disorders was ruled out. A brain MRI was performed and did not show any abnormalities.

After psychiatric stabilization, the patient underwent a middle lobe resection with hilar and mediastinal lymph node dissection.

Postoperative pathology showed a grade I well-differentiated neuroendocrine tumor without histological signs of malignancy: absence of mitosis, vascular emboli and necrosis confirming the diagnosis of a typical carcinoid tumor. Immunohistochemical examination showed positive tumor cells for ACTH, CD56, chromogranin and synaptophysin. The Ki-67 labeling index reached 5%. Melan A and vimentin were negative.

The course, one month after surgery with hormone replacement therapy, was marked by an important clinical improvement, a normalization of blood pressure and blood sugar levels, a collapsed 8-hour cortisol level and a normal serum potassium of 4.2 mmol / L.

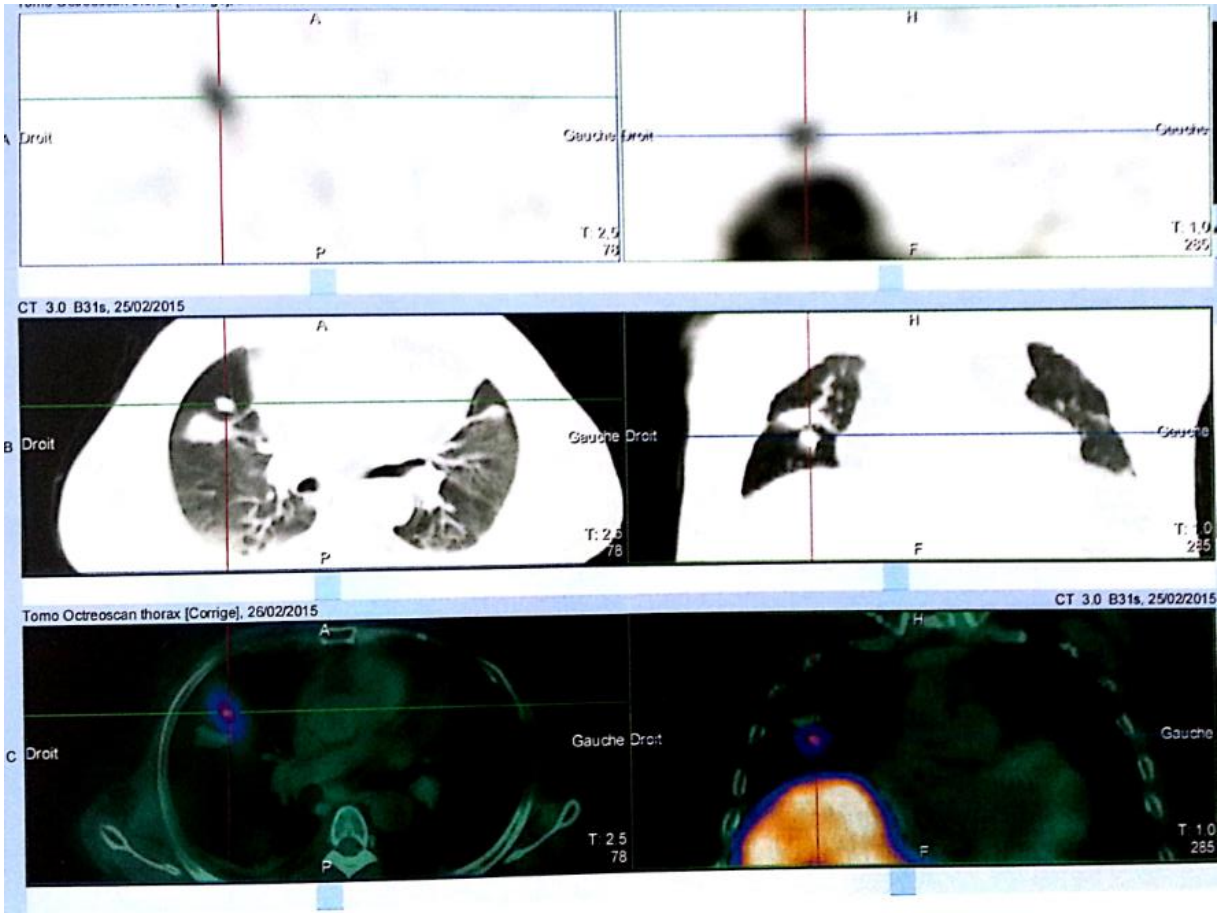

Figure 4: Indium-111-labeled octreotide scintigraphy: significant uptake in the lung nodule.

DISCUSSION

Cushing's syndrome is the clinical expression of a permanent and unbridled hypersecretion of cortisol.

It may be secondary to pituitary or adrenal gland tumor or results from an extra-pituitary secretion of ACTH in paraneoplastic syndromes. This ectopic secretion represents 10 to 17% of cases of ACTH dependent Cushing's syndrome (3,4). Paraneoplastic Cushing's syndrome due to bronchopulmonary carcinoid tumor is rare. Only few case reports and surgical case series has been reported (5).

There is no sex predominance in paraneoplastic Cushing's syndrome, while Cushing's disease is more frequent in young women. The mean age at clinical presentation is in the fourth decade as for our patient and smoking doesn't represent a risk factor (6). Bronchial symptoms are frequent between 52% to 73% of patients according to the series but not constant (7,8). Our patient didn't present any bronchial symptom.

It produces, in its classic form, a major and rapidly evolving hypercorticism, with important signs of protein hypercatabolism, such as osteoporosis, the deterioration in the general condition, hypertension, diabetes and hypokalaemia. Melanoderma is also often associated (1,2,9,10).

In Cushing's disease, the pituitary adenoma is sensitive to the high-dose dexamethasone suppression test, and to corticotropin-releasing hormone (CRH) stimulation test. In the case of ectopic secretion, ACTH and cortisol levels are not influenced by dynamic tests. However corticotropic responses can be observed in up to 40% of patients (6).

The CRH stimulation test is the more specific and sensitive test because cases of ectopic ACTH secretion responding to corticoliberin are exceptional (11).

Several teams advocate combining dexamethasone suppression test and CRH testing. Indeed, a response to both tests makes the diagnosis of ectopic ACTH secretion improbable (12,13).

In the reported case, the CRH stimulation test was not performed, and the high-dose dexamethasone suppression test was negative.

Pituitary MRI should be performed to detect a pituitary adenoma. However, its false-positive rate in the general population is about 10% (14). When the corticotropin-releasing hormone and high-dose dexamethasone test results are positive and the pituitary MRI reveals a 6-mm or larger adenoma, the diagnosis of Cushing's disease can be ascertained. When the results are discordant, it is agreed that bilateral inferior petrosal sinus sampling should be performed (4).

If results of the dynamic tests and may be of catheterization of the bilateral inferior petrosal sinus sampling suggest an ectopic ACTH secretion, the next step, which remains very difficult, is to find the secreting tumor.

In almost half of the cases, the tumor is bronchopulmonary. Next, we find, in a decreasing order of frequency, thymic tumors, pancreatic carcinomas, medullary thyroid cancers and pheochromocytomas. In 30 to 50% of the cases, the tumor remains occult and its topographic diagnosis may escape the conventional imaging techniques (12,15).

Indium-111-labeled octreotide scintigraphy is a standardized reference examination because of the high density of somatostatin receptors in carcinoid tumors (16). It can detect bronchial carcinoid tumors smaller than 1 cm with a sensitivity of 80% (17). It was positive in our case.

The interest of PET-18FDG (positron emission tomography with 18F-fluoro-deoxyglucose coupled with the scanner) in the diagnosis, the localization and the follow-up of these tumors is reported in about ten observations (18,19).

The prognosis of these paraneoplastic Cushing's syndromes is conditioned by metabolic complications such as hypokalemic alkalosis and by the nature of the original tumor (20).

Carcinoid tumors are usually located in the central part of lung (80%) and mainly endobronchial, but they can be nodular and intra-parenchymal as in our observation(21).

Complete resection is the only curative treatment for ACTH secreting bronchopulmonary carcinoid tumors. During the preoperative period, or in case of failure of surgery, medical treatment is based on steroidogenesis inhibitors. Ketoconazole, an imidazole antifungal, is indicated as a first-line treatment. It acts on several enzyme targets associated with cytochrome P450 and is generally well tolerated, but it may cause hepatotoxicity (22).

Bilateral adrenalectomy remains exceptionally indicated, but it allows an immediate cure of hypercorticism in 100% of cases but with need of permanent hormone replacement therapy. Nowadays it is a laparoscopic surgery with no mortality risk and low rates of morbidity. It is indicated in two different situations: in emergency to save patients in case of severe and rapidly evolving Cushing's syndrome; or if the responsible tumor is not found and anti-cortisolic treatment is ineffective.

CONCLUSION

Ectopic ACTH secretions are a rare cause of Cushing's syndrome. The rapidity of the onset of clinical signs and the severity of the complications should suggest a paraneoplastic origin of the Cushing syndrome. It is essential to locate the extrahypophyseal origin of the ACTH secretion, using the various available means of exploration.

AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals of the International Committee of Medical Journal Editors. Indeed, all the authors have actively participated in the redaction, the revision of the manuscript and provided approval for this final revised version.

COMPETING INTERESTS

The authors declare no competing interests.

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