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Ectopic Cushing's Syndrome: About A Defying Case Report and Literature Review

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Abstract **Case Report**

Introduction: Ectopic secretion of Adrno-Cortico-Tropic-Hormone (ACTH) is a rare cause of endogenous hypercorticism. Locating the tumour responsible remains the main and most difficult stage in its management. ***Case report:*** We report the case of a 33-year-old male patient admitted with rapidly progressive flare hypercorticism related to ectopic ACTH secretion. Given the rapid worsening of the clinicobiological picture and the impossibility of locating the causative tumour, a bilateral salvage adrenalectomy was performed. ***Discussion and Conclusion:*** The small size of the tumours responsible for ectopic ACTH secretion sometimes makes them very difficult to localise, necessitating the use of symptomatic rescue treatments.

Keywords: Ectopic secretion, cushing's syndrome, anticortisonic drugs, adrenalectomy.

INTRODUCTION

According to studies, approximately 10 to 20% of cases of cushing's syndrome are secondary to ectopic secretion of ACTH by extra-pituitary tumours, which are, in decreasing order of frequency: bronchial carcinoids, small cell lung carcinomas, thymic neuroendocrine tumours, pheohromocytomas and pancreatic tumours [1]. At the same time, in 30-50 % of cases the source of ectopic ACTH secretion remains hidden [2], posing enormous diagnostic and therapeutic difficulties.

CASE REPORT

A 33-year-old male patient, diabetic and hypertensive 4 months previously, was admitted with a rapidly progressive flare-up of hypercorticism, with a faciotruncal distribution of fat, purple stretch marks on the thigh, fungal infections on the pubic area and armpits, an erythrosic lunar facies and a recent weight gain of 9 kg. The haemodynamic evaluation showed a blood pressure (BP) of 150/110 mmhg, a heart rate of 75 bpm, a respiratory rate (RR) of 19 cpm, a capillary blood glucose level (CG) of 2.88 g/l without ketosis on urine dipstick, a body mass index (BMI) of 26.6 kg/m2, with oedema of the lower limbs reaching to the ankles and taking up the bucket.

The positive diagnosis was based on a 24-hour free urinary cortisol (FUC) of 2912.5 ug/24 h (20.8 times normal), negative minute braking with 1 mg of dexamethasone (DXM) and a disruption of the nycthemeral cortisol cycle with cortisol levels 8h00 pm at 22.7 ug/dl and midnight cortisol at 23.8 ug/dl. ACTH was very high at 147 pg/ml, with a 3*2 mm pituitary micronodular lesion on hypothalamic-pituitary MRI, which was enhanced late (Figure 1).

The latter would not explain the rapid and aggressive onset of Cushing's syndrome in our patient, hence the need for a ThoracoAbdominoPelvic (TAP) CT scan which revealed a subpleural nodule in the ventral segment of the right upper lobe of the lung with irregular contours, a left adrenal nodule measuring 18*17 mm (Figure 2) and negative strong braking with 8 mg of DXM (Cortisol before: 31,1 ug/dl, cortisol after: 21,1 ug/dl therefore a decrease of 32,15%, 24-hour FUC before: 2780 ug/24h, 24-hour FUC after: 1913.88ug/24h, a decrease of 31.15 %). Catheterisation of the petrosal sinuses was not available.

In terms of complications, for hypertension the patient was put on a combination of valsartan-amlodipine 160/10 mg per day, spironolactone 150 mg/day. For diabetes, the insulin regimen was adjusted to 2 premixes of 36 iu in the morning and 42 iu in the

evening, with a rapid insulin of 16 iu at midday and Metformin at 2g a day. Thyroid function tests were normal, with us TSH at 0.5 mIU/l and free T4 at 13 pmol/l. Testosterone levels were low, with low LH at 0.2 and FSH at 0,80, normal prolactine at 16, 26, dyslipidemia with total cholesterol at 2,33 g/l and LDL cholesterol at 1,41 g/l.

Echocardiography and funduscopic examination were without abnormalities. A potassium replacement 1.4 g: 6 tablets per day was introduced. In impedencimetry, Weight was 76.1 kg, with fat at 18.6 kg (24.4%), Muscle mass at 54.6 kg and Lean mass: 57.5 kg. On blood ionogram natremia at 144,14 Kaliemia low at 3,3.

Blood count showed white blood cells at 12150/mm3, hemoglobine at 15,5 g/dl. Creatinine clearance at 132 ml/min, 24-hour microalbuminuria at 71,6 mg/24 h (normal < 30), liver transaminases ALAT/ASAT: 81/24 UI/l, the phosphocalcic test showed a serum calcium at 90.45 mg/l, serum albumin at 42.9 g/l, serum phosphorus at 25.55 mg/l, vitamin D at 20 ng/ml (low), parathyroid hormone at 235 pg/ml controlled after 3 months at 79 pg/ml (normal : 15-68) and 24-hour calciuria at 482.12 mg/24h (normal 100-300), with osteodensitometry showed high fracture risk for the spine and low risk for the femur. Urine osmolality was low at 247.58 mosm/l. Cervical ultrasound showed no thyroid or parathyroid abnormalities.

On the basis of these data, an octreoscan was ordered, which revealed a 9*8 mm left adrenal nodule with tracer fixation (Figure 3). The patient was put on anti-cortisolic treatment based on ketoconazol 600 then 1200 mg per day with good tolerance.

After 2 months, given the deterioration in the patient's clinical condition, a left adrenalectomy was indicated and performed, with a pathological study showing locally micronodular adrenal hyperplasia.

The course was marked by persistent signs of cortisol imbalance, with a 24 h FUC at 271ug/24h (3 times normal), negative minute braking at 22 ug/dl 1 month and 32 ug/dl 3 months after surgery, strong braking test with 8 mg DXM showed 8 a.m. cortisol level at 35 ug/dl befor and 25 ug/dl after test, so a reduction of less than 50%, which is still in favour of the persistence of ECS and hypokalemia at 2.04, the osteoporosis was complicated by rib fractures and vertebral compression.

The appearance of the picoadenoma was satble on pituitary MRI and the TAP- CT scan was normal. The octreoscan was repeated 5 months after surgery, as it did not reveal any tracer-fixing focus. A PET scan with 68 Ga-DOTATOC was indicated but was not performed for lack of means and availability.

Given the worsening of the patient's clinical condition, with an accentuation of the cushing's syndrome (purple stretch marks (Figure 4), bone pain, amyotrophy), and the persistence of profound hypokalemia despite anticortisolic treatment, a salvage right adrenalectomy was indicated with anatomopathological study in favour of diffuse micronodular adrenal hyperplasia without signs of malignancy.

The evolution 3 months after the 2nd surgery was marked by a clear clinical and biological improvement with normalisation of glycaemia, blood pressure and a normal kalaemia at 3,6 (Figure 5).

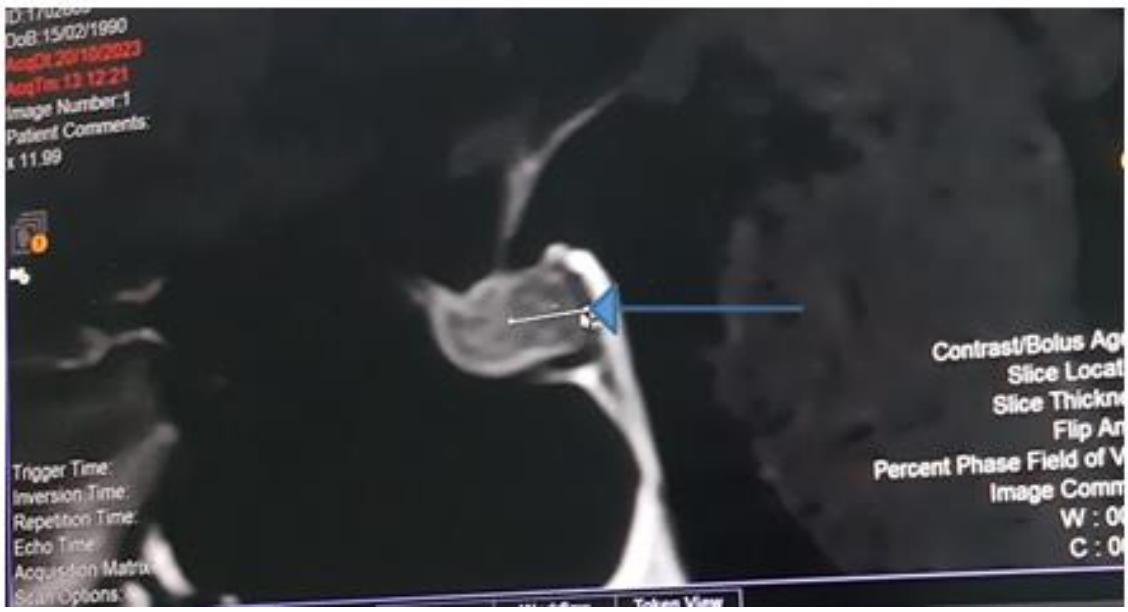

Figure 1: Hypothalamic-pituitary MRI : 3*2 mm picoadenoma of left lobe

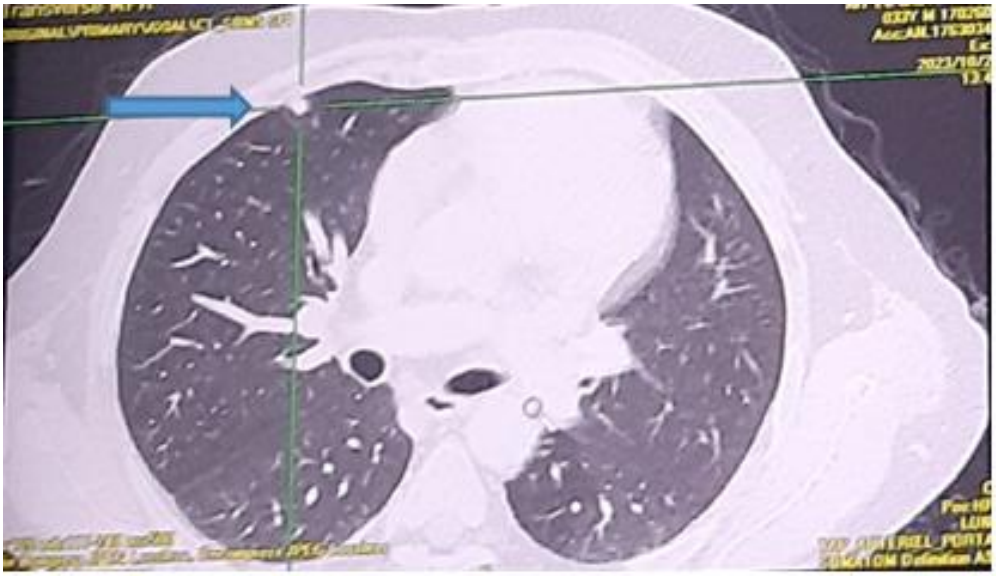

Figure 2: TAP CT scan: nodule of upper lobe of the right lung (18*17 mm)

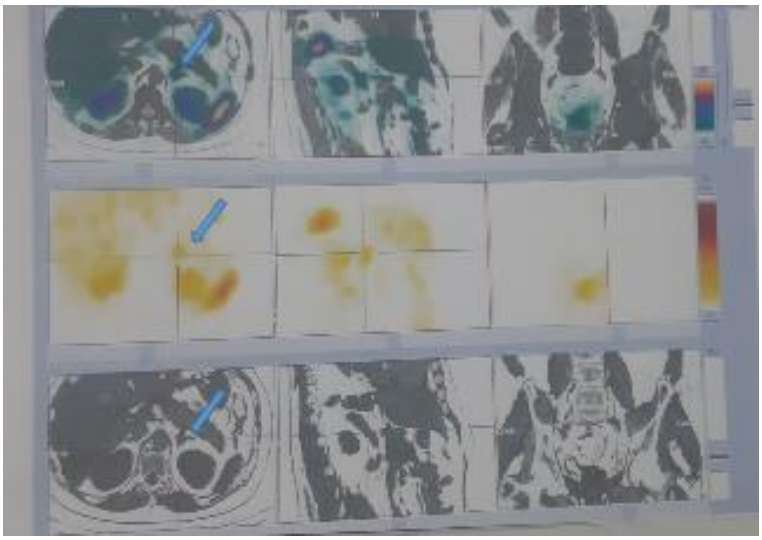

Figure 3: Octreosca: tracer hyperfixation in a left adrenal nodule (9*8 mm)

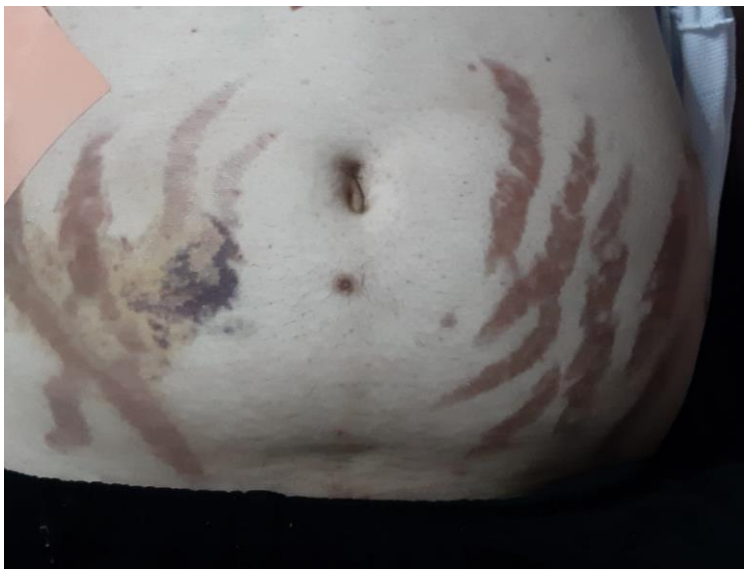

Figure 4: Abdominal purple stretch marks

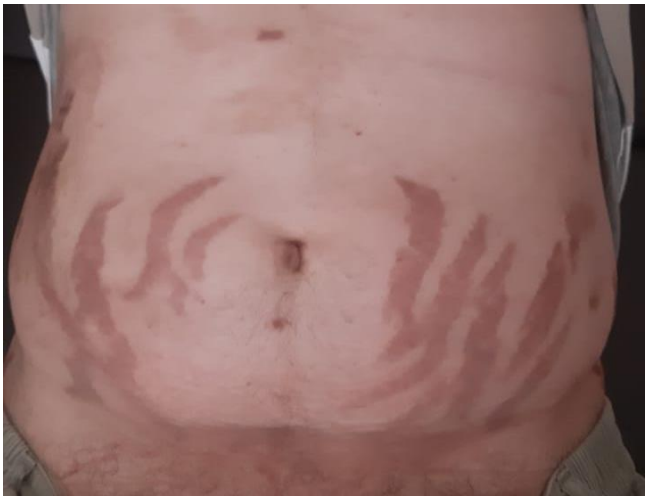

Figure 5: Abdominal purple stretch marks 3 months after the 2 nd surgery

DISCUSSION

Cushing's syndrome (CS) is the result of pathological cortisol hypersecretion [3]. It is a rare clinical condition with an estimated annual incidence of 3 cases per million [4]. CS can be either exogenous, due to the use of glucocorticoids for medical purposes or self-medication, or endogenous, due to ACTH secretion by an anteropituitary adenoma known as cushing's disease (CD) in 50 to 80% of cases, or an adrenocortical adenoma with autonomous cortisol secretion in almost 15 to 25% of cases [3, 4].

Ectopic secretion of ACTH responsible for what is known as paraneoplastic endogenous cushing syndrome or ectopic cushing syndrome (ECS) is incriminated in 10 to 20% of cases, secondary to neuroendocrine tumours located mainly in the lung, thymus, pancreas and adrenal gland.

There was no predominance of ECS in one of the 2 sexes, which differentiates it from cushing's disease, characterised by a clear female predominance of around 80% of cases [5].

The clinical presentation of ECS varies according to the severity of the hypercortisolism and how long it has been installed. The clinical features are mainly weight gain, arterial hypertension, glucose intolerance or even diabetes mellitus, muscular fatigability predominating in the limbs, osteoporosis with fractures of the ribs and vertebrae and depression [6]. Melanoderma is often found due to high circulating levels of melanocyte-stimulating hormone (MSH), derived from the cleavage of ProOpioMelanoCortin (POMC). If hypercortisolism is immediately evident, the patient will present with treatment-resistant hypertension, profound hypokalemia, accentuated insulin resistance and muscular atrophy, sometimes leading to bed rest [7]. In moderate forms, the clinical picture of ECS may be identical to that of cushing's disease, making a differential diagnosis difficult [8].

Although the most recognised aetiologies of ECS are bronchial neuroendocrine neoplasia (20-40%), small cell lung carcinoma (10-40%), pancreatic (10-20%) or thymic (5-10%) neuroendocrine neoplasia, pheochromocytoma (2-6%), medullary thyroid carcinoma (2-10%) [9], the ectopic source of secretion remains hidden in more than 20% of cases [1], this underlines the importance of functional localisation imaging techniques in identifying these tumours [10].

In our patient, the clinical picture was rapid and aggressive in onset, with bilogical evidence of severe hypercortisolism, in particular FUC approaching 3000 ug/ 24h, ACTH elevated to 147 pg/ml and profound and persistent hypokalemia sometimes reaching 1.7 meq/l, all of which was in favour of ECS. Despite the initial visualisation of an upper lobar nodule of the right lung on the TAP scan, and the image of the pituitary picoadenoma on the hypothalamohypophyseal MRI, complementation by Somatostatin receptor scintigraphy (octreoscan) did not show hyperfixation at these 2 levels, but it did objectify the left adrenal nodule previously described. It was therefore not possible to link this ECS with certainty to the pulmonary or pituitary lesions.

Octreoscan usually plays an important role in locating the primary tumour responsible for ectopic ACTH secretion, based on the fact that many neuroendocrine cells express this type of receptor, known as SST-R 1 to 5, with the SST-R 2 subtype as the main target of this test, This is because the affinity is greater for these SST-R 2 than for subtypes 3 and 5, whereas it is nil for subtypes 1 and 4. These SST-R2 has been identified on the majority of neuroendocrine tumour cells and their metastases [11].

The principle of this functional imaging examination is based on the use of a tracer (somatostatin analogue) coupled with a radioactive marker which, once the tracer-marker pair is attached to its receptor, emits gamma radiation that is detected by a gamma camera.

Several markers can be used in octreoscan, mainly indium 111 with as chelator the diethlene-triamine-pentaacetic acid (DTPA), thus forming the [111In-DTPA] octreotide couple [12]. In our patient we used 99mTc-labelled Tektrotyd. The sensitivity of octreoscan ranges from 82 to 95 % it depends of tumour size, presence and density of type 2 and type 5 somatostatin receptors on its surface and the heterogeneity of expression of these receptors, which explains the relatively high percentage of false negatives reaching 10 to 20% of cases due to the absence of SST R2, their low density or the small size of the tumour ; which underlines the main advantage of combining octreoscan with single-photon tomography (TEMP) and computed tomography (CT), to improve sensitivity, for better localisation of fixation foci, for correction of the attenuation of gamma photon and to increase lesion contrast within the image [13-16].

It should be borne in mind that a significant number of neuroendocrine tumours do not express SST-R, which is why positron emission tomography (PET) has been used in recent years to identify NEN, as well as liver, bone and lymph node metastases and several high-performance tracer-label pairs are used, in particular 18F-Fluorodihydroxyphenylalanine (18F-dopa), 68Ga-DOTA-Tyr3-Octreotide (68Ga-DOTATOC) and 68Ga-DOTA-Tyr3-Octreotate (68Ga-DOTA-TATE). Given the unavailability of this examination in our centre and the lack of resources, it was indicated but not carried out [17-19].

In addition to the functional imaging techniques mentioned above, fairly complex blood tests requiring a heavy technical platform can be used to distinguish between CD and ECS. This is the case for venous catheterism of the inferior petrous sinuses, making it possible to search for an ACTH secretion gradient between the juxtaposed veins. In the absence of any CRH stimulation, an ACTH gradient greater than 2 indicates CD, whereas a gradient of less than 1.4 indicates ECS. After stimulation, if the gradient is greater than 3, the diagnosis of CD is almost 100%. In the absence of a gradient, the aetiological diagnosis is directed towards ECS, even if the tumour is occult, as has been several recent studies [20-22]. Unfortunately this catetherism was not performed on our patient due to lack of availability.

If the primary tumour responsible for the ectopic secretion of ACTH is not identified, several teams recommend that the patient be put on anticortisolic medical treatment and monitored for 6 to 12 months, using morphological, pituitary and thoracic tests to look for the tumour in order to identify it.

Despite the patient being put on ketoconazole with management of the complications of hypercoticism, i.e. diabetes, hypertension, osteoporosis, hypokalemia, and given the impossibility of locating the tumour responsible, the worsening of the patient's clinical condition led us to recommend bilateral rescue adrenalectomy in two stages.

CONCLUSION

Tumors responsible for ectopic secretion of ACTH are a rare cause of cushing's syndrome. The noisy, rapidly-onset clinical picture and the severity of hypercortisolism and complications testify to ectopy as the secretory origin. The major obstacle faced by clinicians is tumor localization, and despite fairly high-performance functional imaging techniques, these tumors sometimes remain occult, necessitating aggressive treatments such as bilateral salvage adrenalectomy.

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