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An Ectopic Cushing's Syndrome with Severe Psychiatric Presentation: A Case Report

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Abstract

Ectopic ACTH Secreting (EAS) tumor is relatively rare entity that presents with severe manifestation due to high level of endogenous hypercortisolism and rapidity of its onset. We report a case of severe EAS in a young Tunisian man resulting from a well differentiated Neuroendocrine Tumor (NET) of the lung. Besides catabolic signs and profound hypokalemia orienting towards Cushing's Syndrome (CS), psychiatric symptoms were particularly severe, dominant and atypical including persecutory delusions, depression and anxiety. After tumor localization, successful resection was performed and the majority of psychiatric symptoms resolved rapidly except for mild depression.

Keywords: Cushing's syndrome; Neuroendocrine tumor; Ectopic ACTH secretion; Psychiatric presentation; Hypokalemia; Tunisia

Introduction

Cushing's Syndrome (CS) is defined by a pathological hypercortisolism resulting from Adrenocorticotropic Hormone (ACTH) excessive production or autonomous adrenal cortisol production. It is associated with significant comorbidities and considered a potentially lethal disorder [1].

CS due to Ectopic ACTH Secretion (EAS) is infrequent, representing between 9% and 20% of ACTH-dependent CS [2-4] and 5% to 10% of all types of CS [5]. EAS is associated with severe hypercortisolism resulting from unregulated ACTH expression and secretion by Neuroendocrine Tumors (NETs) that causes massive cortisol secretion by the adrenal cortex [2]. Psychiatric symptoms are common but unusual initial manifestation [6]. Metabolic complications are particularly severe, especially profound hypokalemia that could be more suggestive of EAS [7].

We describe a challenging case of EAS with severe psychiatric symptoms and profound hypokalemia in a young male.

Case Presentation

A 36-year-old man, with one-year history of Diabetes Mellitus (DM), was referred to our department in July 2019 due to severe Hypertension (HT) and profound hypokalemia.

He presented with recent changes in physical appearance in the last four months including truncal weight gain, fatigue, insomnia and abnormal gait.

Physical examination showed cushingoid features including rounded face, buffalo hump, violaceous abdominal and axillary striae, bruising, weakness in the proximal muscle groups with lower limb amyotrophy and Tinea Versicolor on the back (Figure 1). He had resistant HT requiring four antihypertensive medications including spironolactone. Psychiatric assessment revealed emotional lability, depression, anxiety and persecutory delusions.

Routine blood tests revealed severe hypokalemia and impaired fasting glucose (Table 1).

Hypokalemia was severe and associated with Electrocardiogram (ECG) changes including T-wave flattening and inversion and it required intravenous chloride potassium infusion with 600 mg of Spironolactone daily in order to overcome the renal loss. Fluconazole 400 mg was not sufficient to control hypercortisolism.

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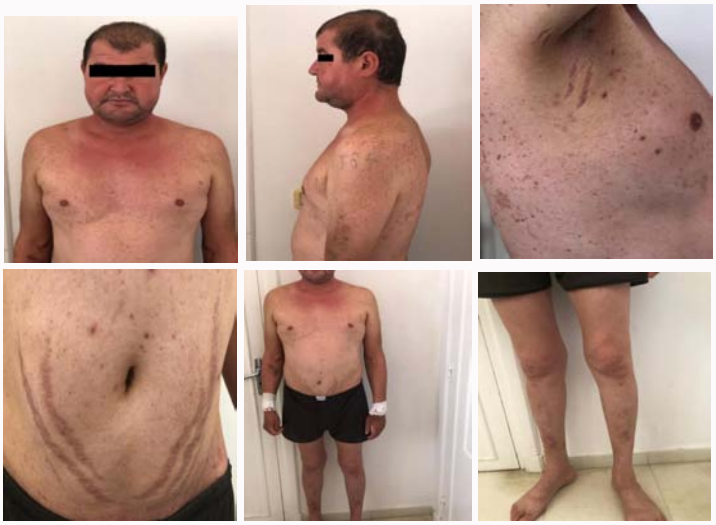

Figure 1: Patient preoperative phenotype.

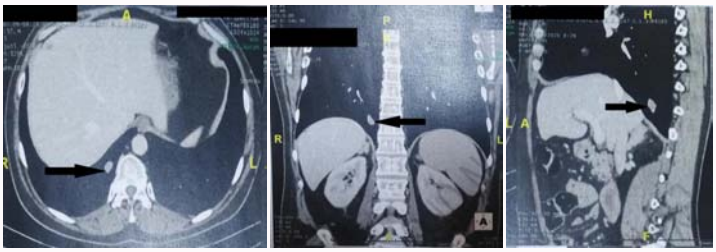

Figure 2: Chest CT scan.

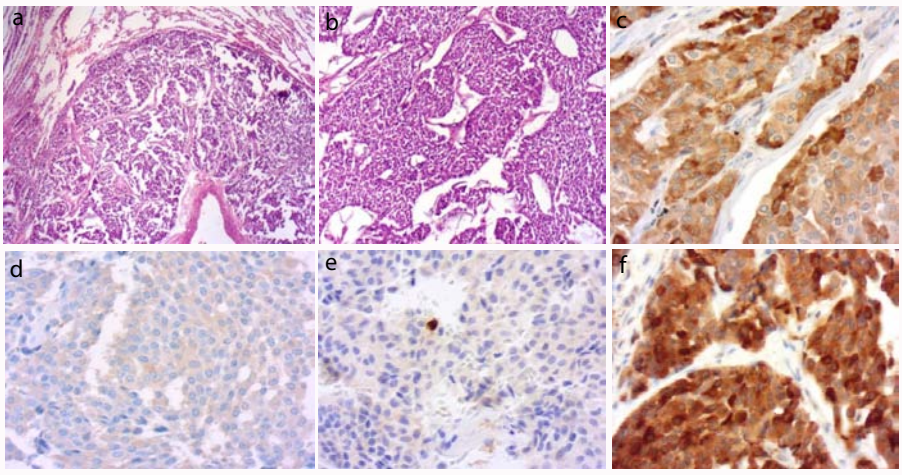

Figure 3: Histology. (a, b) Tumoral proliferation. (c) Positive Chromogranin A immunostaining. (d) Positive Synaptophysin immunostaining. (e) Ki-67 proliferation index 1%. (f) Positive ACTH immunostaining.

As clinical suspicion of endogenous hypercortisolism was high, hormonal tests revealed a significant increased level of 24 h Urinary Free Cortisol (UFC) excretion and altered cortisol circadian rhythm. Elevated morning plasma Adrenocorticotropic Hormone (ACTH) level oriented towards ACTH-dependent CS. Low-dose and high-dose dexamethasone (8 mg at 11 pm on day 1) suppression tests were both negative making the diagnosis of EAS very suspected (Table 2). Chromogranin A level was high (147 ng/mL), indicating in favor of NET.

Pituitary Magnetic Resonance Imaging (MRI) showed no identifiable tumor and Bilateral Inferior Petrosal Sinus Sampling (BIPSS) as well as CRH test were not performed (not actually available in our country).

Chest CT scan revealed one nodular homogenous lesion in the posterior lower lobe of the right lung measuring 20 mm (spontaneous density 25 HU) (Figure 2). Abdominal CT showed bilateral adrenal hyperplasia.

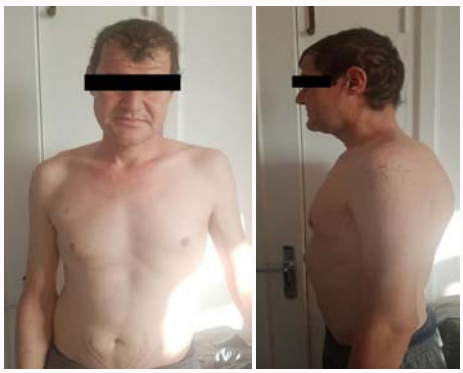

Figure 4: Postoperative phenotype.

Table 1: Routine laboratory results.

Analyses	Results	Reference values
Sodium	131	136-145mmol/l
Potassium	2.7	3.5-5.5 mmol/l
FPG	8	4-6 mmol/l
HBA1C	10.3	4.5-6.5%
Creatinine	53	53-120 µmol/l

FPG: Fasting Plasma Glucose

Table 2: Hormonal laboratory results.

	Results	Reference values
Serum cortisol 8 a.m.	499	100-250 µg/L
Serum cortisol 4 p.m.	428	100-250 µg/L
Serum cortisol midnight	351	100-250 µg/L
24-hour UFC	3880	11-73 µg/24 h
ACTH 8 a.m.	245.4	10.3-48.3 pg/mL

The patient underwent a video-assisted thoracoscopic surgery with total resection of the tumor. Histology revealed a 1.7 cm grade 1 NET (chromogranin A + synaptophysin +, Ki-67 proliferation index 1%) with a positive immunostaining for ACTH (Figure 3).

In postoperative course, serum potassium level was spontaneously within the normal range and all antihypertensive drugs were discontinued due to normalization of blood pressure. Plasma ACTH and 24 h-UFC normalized and 20 mg hydrocortisone supplementation was initiated. After 4 months of surgery, the patient is still free from disease recurrence and on Metformin therapy for his DM. Psychiatric assessment revealed improvement of delusions but persistent moderate depression (Figure 4).

Discussion

EAS, also called paraneoplastic CS, results from unregulated ACTH secretion by NETs and represents between 9% to 20% of cases of ACTH-dependent CS [2,3].

NETs are relatively rare and heterogeneous neoplasms representing between 0.5% and 2% of all malignancies [8]. They result from widely dispersed Neuroendocrine (NE) cells found in endocrine glands (pituitary, parathyroid and NE adrenal), thyroid and pancreatic endocrine islet tissue and endocrine tissue of the digestive and respiratory tracts.

This patient presented with severe persecutory delusions that improved dramatically after the surgery. Notwithstanding, neuropsychiatric clinical signs of CS commonly described are depression (50-81%), anxiety (12-79%) and memory impairment. Infrequently psychosis and mania are present (8% and 3% respectively) and psychosis occurs more likely with malignant tumors. Apparently, hippocampus damage secondarily to multiple phenomena may explain these signs and particularly psychosis seems related to an enhance dopaminergic activity [6,12]. In this case, psychotic signs may be associated to the dramatically high level of UFC.

Luckily for this patient, delusions resolved after successful surgical treatment while moderate depression persisted. In fact, neuropsychiatric pathology may persist for several years after biochemical remission from CS such as maladaptive personality, attention and memory [6,10]. In a recent study, Schernthaner-Reiter et al. found a surprising fact that lower baseline UFC level at diagnosis is associated with long term persistence of comorbidities including neuropsychiatric ones. In fact, lower UFC level is associated with long duration of exposure to cortisol and delay of diagnosis [10].

Hypokalemia defined as plasma potassium <3.5 mmoL/L was particularly profound and it required continuous intravenous infusion and ultimately spironolactone. In a recent study of 58 cases of EAS, Torpy et al. found a significant positive correlation between hypokalemia and the level of UFC. The presumed underlying mechanism is mainly the mineralocorticoid action of supraphysiological cortisol levels that saturates the inactivating enzyme (11β-hydroxysteroid dehydrogenase 11β-HSD2). An inhibitory effect of ACTH itself on the 11β-HSD2 is also suggested [11].

Interestingly, this small low-grade NET was associated with a severe hypercortisolism which initially oriented towards an aggressive tumor. Besides, the patient had not skin hyperpigmentation in the spite of the high level of ACTH. This condition is present in 19% to 88% of EAS and seems to be related more to its severity and rapidity of onset than to its duration. Small Cell Lung Carcinoma (SCLC) and metastatic tumors are more likely to be associated with skin hyperpigmentation [12,13].

The diagnosis of EAS was challenging in this case not only because of its clinical heterogeneity and severity of hypercortisolism but most importantly the difficulty of management during the time of COVID-19 pandemic and the lockdown. It was also important to differentiate it from Cushing Disease (CD) and ectopic Corticotropin-Releasing Hormone (CRH) secretion. High Dose (8 mg) Dexamethasone Suppression Test (HDDST) was negative and oriented towards the diagnosis of EAS but its diagnostic accuracy is considered low. Plus, the combination of HDDST and CRH stimulation test may have great utility for distinguishing between CD and EAS [14]. Unfortunately, CRH and desmopressin stimulation tests were not available. There were no identifiable adenoma or pituitary hyperplasia on MRI but it was important to keep in mind that more than 40% of CD may have negative MRI. In this latter situation, BIPSS in consensually indicated [14] but was also not available. Besides all these difficulties, we considered the rapid onset of clinical signs, the weight loss and the higher levels of ACTH and cortisol to reinforce the diagnosis of EAS [5]. Moreover, CRH ectopic syndrome was very unlikely and it is indeed a very rare condition with few reported cases in the literature [2,15].

Due to its size and site, this bronchial tumor had no respiratory symptoms. Despite this fact, it was identified by a high-resolution

CT scan as most of NETs responsible of EAS are located in the chest [2]. Tumor localization can be difficult as more than 30% of EAS are occult and nuclear medicine imaging is needed especially 68Ga-DOTA-Somatostatin Analogue (SSA) PET/CT. This latter technique has indeed a great sensitivity for detection of covert EAS as well as metastases and synchronous NETs [14].

Conclusion

We reported a case of EAS in a young Tunisian male with initial severe psychiatric presentation and resistant hypokalemia. CS should be considered by clinicians in the presence of atypical disease presentation mainly psychosis, DM and HT.

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