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Management of An Ectopic Cushing Syndrome Case During The COVID-19 Pandemic

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Abstract

Cushing's syndrome (CS) due to ectopic adrenocorticotropic hormone (ACTH) secretion is an infrequent form of ACTH-dependent Cushing's syndrome but a severe condition associated with the highest mortality rate among all causes of endogenous Cushing's syndrome. Differentiating Ectopic Cushing Syndrome (ECS) from Cushing's disease (CD) remains challenging. We, hereby, describe the case of a 29-year-old man with an ACTH-dependent Cushing syndrome presenting with severe hypercortisolism comorbidities. The patient was referred to the hospital during the first phase of Coronavirus Disease 2019 (COVID-19) pandemic. During hospitalization, an Acute Respiratory Syndrome associated with Pneumocystis Jirovecii infection introduced difficulties in terms of differential diagnosis, complicated the patient's clinical status, and hindered access to specific diagnostic procedures. Failure to control cortisol secretion, in the setting of an occult tumour, dictated a life-saving bilateral adrenalectomy. After the clinical recovery, a 68Ga-DOTANOC PET/CT was performed and a peri-centimetric mediastinal tumour was identified.

Keywords: *COVID-19, Ectopic Cushing Syndrome, Endocrine Tumour*

Introduction

ECS is an infrequent form of ACTH-dependent Cushing's syndrome, caused by ACTH or rarely, by corticotropin-releasing hormone (CRH) secreting tumours.[1-3] ECS represents around 10% to 20% of ACTH-dependent Cushing's syndrome cases [4, 5].

The lung is the primary site of 50% of cases (bronchial neuroendocrine tumours and small cell lung cancer). Other sources include thymic and enteropancreatic neuroendocrine tumours, pheochromocytoma and medullary thyroid carcinoma [5].

ECS is a heterogeneous disease resulting from tumours with various degrees of histological differentiation and aggressiveness. Tumoral aggressiveness and intensity of cortisol secretion may be dissociated.[3] Well differentiated neuroendocrine tumours (NETs) mainly secrete mature and bioactive 1-39 ACTH while less differentiated NETS and neuroendocrine carcinomas (NECs) may secrete unprocessed POMC.

Identify the ACTH / CRH ectopic source can be particularly challenging. Up to 20% of ACTH-secreting tumours remain occult [6, 7].

The optimal treatment of the ECS is surgical resection of the tumour with curative intent. However, in the absence of a topographic diagnosis, medical treatment is the unique option. In patients unresponsive to medical treatment, bilateral adrenalectomy might be indicated aiming to avoid a dismal outcome [3, 5].

Hypercortisolism is associate with cardiometabolic and immune impairments and the cardiovascular risk and the increased susceptibility to infections are the main causes of death.

Management of this case, during the first phase of COVID-19 pandemic was, therefore, specially challenging.

Case Presentation

The patient, a 29-year-old German male living in Portugal for one year, was transferred to our hospital, a Public Tertiary Referral Centre, after being 2 months in a private hospital. His first hospitalization aimed to establish the cause of a severe clinical Cushing's syndrome and to control associated comorbidities. The history was remarkable for a 20 kg weight gain in the last 3 years in parallel with complaints of middle and lower back pain that conducted to the diagnosis of several vertebral fractures. Later on, he was diagnosed with arterial hypertension and Diabetes *Mellitus* type 2. Always refused treatment. He was a smoker of 5-pack-years and denied alcohol intake and illicit drugs use. The family history was unremarkable.

Treatment was started with potassium chloride 1200mg 3id, spironolactone 400mg id, valsartan 240mg id, nifedipine 60mg 2id, carvedilol 12,5 mg 2id, low molecular weight heparin 40mg id, pantoprazole 20mg id, calcium carbonate plus colecalciferol 1500mg plus 400mg 2id, transdermic buprenorphine 35mcg, metamizole 575mg 3id and glargine insulin 36 units.

One month before referral to our hospital, an acute cholecystitis dictated a cholecystectomy. Before surgery, the patient was tested by nasopharyngeal swab (quantitative RT-PCR) for COVID-19. The first 2 tests were indeterminate and the third positive. No clinical features suggestive of disease such as cough, dyspnoea, anosmia, ageusia, conjunctivitis or diarrhoea were present. A chest CT showed passive atelectasis in both lung bases. Surgery underwent uneventfully. Following surgery, SARS-CoV2 screening tests at day 4 and day 7 were repeated and both were negative. Later on, the patient started persistent symptoms of dyspnoea with documented type 1 respiratory failure and was then transferred to our hospital.

At first observation, a Cushing phenotype was observed: central adiposity, purple abdominal striae, full moon face and facial plethora. The patient was bedridden as a consequence of marked myopathy. He was apyretic, had a blood pressure of 161/89mmHg, heart rate of 98bpm, peripheral saturation of 96% (fraction of inspired oxygen of 36%). The respiratory auscultation showed a globally decreased vesicular breath sound and wheezes in the right thorax. Cardiovascular and abdominal examinations were unremarkable.

The initial analytical profile was: leucocytes $13.38x10^9$/L, neutrophils $12.48 x10^9$/L, lymphocytes $0.37x10^9$/L, normal C-reactive protein (CRP) (0.12mg/dL), D-dimer levels (0.22µg/mL) within the reference range, and no abnormalities in coagulation tests.

Progressively, there was a need to increase oxygen flow rate and a new chest CT showed a ground-glass opacification pattern with perilobular and peribronchial distribution in all lobes. A bronchofibroscopy was performed and a bronchoalveolar lavage (BAL) analysis identified a *Pneumocystis Jirovecii* by PCR test and treatment was adjusted to this finding. The screening of SARS-CoV2 in pulmonary secretions was negative.

At same time, a basal endocrinological evaluation was conducted and the results were: ACTH 130pg/mL, similar morning and night serum cortisol 50.4ug/dL, TSH 0,219 uU/mL, FT4 0,77 ng/dL, FSH 0,5 U/L, LH < 0,1 U/L, total testosterone 81.9 ng/dL, normal prolactin levels and 24-hour urinary free cortisol 2964pg/24h. From the general biochemical assessment, a severe hypokalaemia (potassium 2,7mmol/L) is highlighted. The glycated haemoglobin was 7.8%.

A corticotropin hormone (CRH) stimulation test, performed during the first hospitalization, documented a 28% increase of ACTH, 30 minutes after stimulation. Pituitary MRI was interpreted as negative.

Thereafter, a bilateral inferior petrosal sinus sampling (BIPSS) was performed in which ACTH levels before and after CRH stimulation were measured. No gradient between central and peripherical values of ACTH was noted (Table 1).

ACTH (pg/ml)	Baseline	5 min	10 min	15 min
Peripheral vein	44,7	---	39,5	35,5
Right petrosal sinus	67	63,8	55,3	45,9
Left petrosal sinus	56,6	66,3	51,2	43,9
BIPSS-bilateral inferior petrosal sinus sampling; CRH – corticotropin-releasing hormone				

Table 1: Levels of ACTH measured during BIPSS after CRH.

Based on the clinical severity, in the presence of marked hypokalaemia and on the BIPSS results the most likely diagnosis was an ectopic source of ACTH. Towards a topographic diagnosis, a whole-body CT and a 99mTc-Octreotide were performed and were deemed negative.

Differential Diagnosis

Distinction between Cushing's disease and an ectopic Cushing's syndrome is not easy based on clinical grounds. Severe amyotrophy, severe hypokalemia and life-threatening infections are seen more frequently in patients with Cushing's syndrome due to an ectopic secretion of ACTH and/or CRH. In the past, the differential diagnosis relied mainly in dynamic hormonal tests. Nowadays they

are still performed but the role of bilateral inferior petrosal sinus sampling and functional imaging became unquestionable.

The CRH test elicited an ACTH response near the cut-off established for Cushing´s disease however, the pituitary MRI did not disclose any microadenoma. A negative MRI may occur in up 40% of Cushing's disease cases. In the current case, due to the aggressiveness of Cushing's syndrome and the severe hypokalemia was important to rule out the hypothesis of an ectopic Cushing. The next step was therefore the BIPSS that enabled the conclusion of the absence of central to peripheral ACTH gradient, thus reinforcing the hypothesis of an ectopic source of ACTH.

When the ectopic secretion of ACTH is associated with a neuroendocrine carcinoma it does not, usually, represent a problem in terms of localization. In contrast, when the source is a well-differentiated neuroendocrine tumour, usually small in size, it may not be revealed by anatomic imaging modalities, as occurred in the present case. Considering the presence of somatostatin receptors (SRs) in these tumours, a somatostatin receptor scintigraphy (SRS) is a useful, noninvasive method providing a whole-body imaging. The patient underwent a 99mTc-Octreotide and no abnormal uptake was observed.

Due to the COVID-19 pandemic, whether the respiratory failure, that progressed to type 2, was due to SARS-CoV2 (nasopharyngeal swab negative) or to an opportunistic infection was definitely clarified by a bronchofibroscopy; analysis of the bronchoalveolar lavage identified *Pneumocystis Jirovecii* by PCR whereas screening of SARS-CoV2 in pulmonary secretions was negative.

Treatment, Outcome and Follow-up

Since the first day of admission, the patient started treatment with metyrapone 250mg 6/6h that was adjusted to 8/8h due to hepatocellular and cholestatic liver injury pattern. The serum cortisol level was as high as 67ug/dL after 1 week of treatment and no clinical improvements were noticed. Potassium chloride was started as intravenous perfusion due to severe hypokalemia. The anti-hypertensive, anti-hyperglycaemic, and analgesic treatments remained the same the patient was undergoing on admission.

During the first weeks of admission, there was a need to increase the oxygen-therapy until a flow-rate of 10L/min. During the night period non-invasive mechanical ventilation was necessary. The patient was admitted in an intermediate care unit. After Pneumocystis *Jirovecii* identification, the patient started trimethoprim plus sulfamethoxazole (TMP-SMX) 800mg plus 160mg 12/12h which was kept for 21 days.

The unresponsiveness to the treatment with metyrapone in parallel with the occurrence of a hepatocellular and cholestatic pattern, and the deterioration of the clinical condition imposed a lifesaving bilateral adrenalectomy. One month after admission to our hospital, a bilateral adrenalectomy was performed. Surgery elapsed without complications. Histology of both adrenal glands revealed diffuse hyperplasia of adrenal cortex. Immediately after surgery, he started treatment with glucocorticoids. As glucocorticoids were tapped fludrocortisone was added.

After bilateral adrenalectomy, there was blood pressure and glycemia normalization. A progressive improvement of purple striae was noted as well as a weight loss of 15kg (along 3 months). Resolution of hypogonadism was documented - testosterone 730ng/dL. After stopping TMP-SMX, the patient had a total recovery of respiratory status and no need of oxigenotherapy or nocturnal non-invasive mechanical ventilation. A program of physiotherapy was initiated with progressive ambulation recovery. One month after the surgery, under treatment with glucocorticoid and fludrocortisone, despite adequate levels of serum cortisol, ACTH levels remained high - 107pg/mL.

Six months after the adrenalectomy, a ^{68}Ga-DOTANOC PET/CT was requested and performed in another institution. A single uptake focus (max SUV = 11) was documented on the right mediastinum corresponding to a peri-centimetric nodule localized on pericardial fat. He is now awaiting surgery (Figure 1).

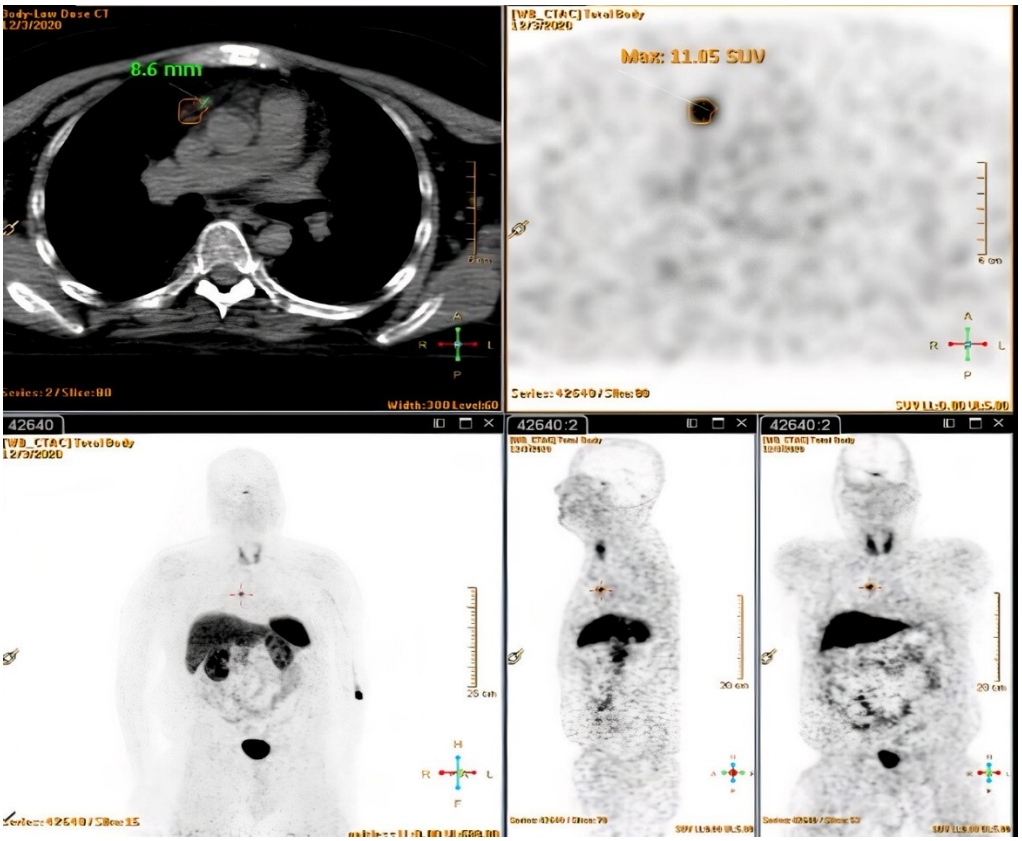

Figure 1: 68Ga-DOTANOC PET/CT. A single uptake focus (max SUV = 11) on the right mediastinum corresponding to a peri-centimetric nodule localized on pericardial fat.

Discussion

Cushing's disease is the most common form of ACTH-dependent Cushing's syndrome. In the case presented herein, integration of all data made us to consider the diagnosis of ectopic Cushing's syndrome the most likely one. Attempts for the localization of the source of ectopic ACTH secretion, aiming to avoid bilateral adrenalectomy, failed.

It is possible to detect ACTH-secreting neuroendocrine carcinomas by means of axial imaging with contrast-enhanced CT, MRI, and scintigraphic studies in 70% to 90% of cases [7]. However, well differentiated neuroendocrine tumours are difficult to detect through CT scan due to their small size. In these cases, functional imaging is particularly helpful. ^{68}Ga-SSTR PET/CT is superior to octreoscan in detecting small neuroendocrine tumours [3, 8] but was unavailable at our hospital and transporting the patient to another hospital was at high risk.

Hypercortisolism may cause an immunocompromised state dependant on the cortisol levels. Cushing's syndrome associated infections include all kinds of opportunistic infections due to bacteria, virus and fungi, including *Pneumocystis Jiroveci, Aspergillus Fumigatus,* and *Cryptococcosis* [9]. Classical symptoms and signs of an infection such as fever and increased levels of C-reactive protein may be lacking.

The behaviour of SARS-CoV2 in patients with Cushing's syndrome is still not established. These patients are likely more susceptible to the infection that may present a poorer prognosis [10].

The present case was particularly challenging, not only in respect to the differential diagnosis of the respiratory distress syndrome, considering a past positive SARS-Cov2 test and CT chest images compatible with the infection, which ultimately was not confirmed since the bronchoalveolar lavage identified Pneumocystis Jirovecii by PCR whereas screening of SARS-CoV2 in bronchial secretions was negative, but also because it was possible to overcome the difficulties inherent to a pandemic scenario and successfully manage a case that was intrinsically associated with a poor prognosis.

Bilateral adrenalectomy was the necessary choice after failure to control cortisol secretion using metyrapone, a specific inhibitor of 11β-hydroxylase.[11] Adrenalectomy is indicated for rescue treatment in very severe hypercortisolism cases, when steroidogenesis inhibitors are ineffective or poorly tolerated and the source of ACTH/CRH secretion is not identified [3].

Following the resolution of the hypercortisolism and recovery of the patient, it was possible to request a ^{68}Ga-DOTANOC PET/CT that disclosed an abnormal single uptake focus on the mediastinum likely to correspond to the source of ectopic secretion of ACTH. The patient is waiting for surgery.

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