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CASE REPORT

AN ECTOPIC ACTH-SECRETING TUMOUR AFTER ADRENALECTOMY FOR PRIMARY ALDOSTERONISM

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Abstract

Introduction. Ectopic adrenocorticotropic hormone syndrome (EAS) is a rare cause of endogenous ACTH-dependent Cushing's syndrome. EAS occurs in about 5–10% of all patients with ACTH-dependent hypercortisolism, with most of cases caused by intrathoracic neoplasms. Tumour detection is still a challenge and often requires multiple imaging procedures.
Case presentation. We describe a case of an ectopic ACTH secretion several months after left laparoscopic adrenalectomy for primary aldosteronism. A 21-year-old male patient presented with severe hypertension, hypokalemia as the first clinical manifestations of an ACTH-secreting lung neuroendocrine tumour, with the typical phenotypic features of Cushing's syndrome. Six months before, the same patient underwent a right laparoscopic adrenalectomy for primary aldosteronism, confirmed by clinical, biochemical, radiological, and histopathological findings.
Conclusions. Neuroendocrine tumours are rare, difficult to diagnose and have a poor prognosis when

Résumé

Une tumeur ectopique sécrétrice d'ACTH après surrénalectomie pour aldostéronisme primaire

Introduction. Le syndrome de l'hormone adrénocorticotrope ectopique (EAS) est une cause rare du syndrome de Cushing endogène dépendant de l'ACTH. L'EAS survient chez environ 5 à 10% de tous les patients atteints d'hypercortisolisme dépendant de l'ACTH, la plupart d'entre eux étant causés par des néoplasmes intrathoraciques. La détection des tumeurs reste un défi et nécessite souvent plusieurs procédures d'imagerie.
Présentation du cas. Nous décrivons un cas de sécrétion ectopique d'ACTH quelques mois après une surrénalectomie laparoscopique gauche pour hyperaldostéronisme primaire. Un patient masculin de 21 ans est présenté pour une hypertension sévère et hypokaliémie, comme premières manifestations cliniques d'une tumeur neuroendocrine pulmonaire sécrétant de l'ACTH, avec les caractéristiques phénotypiques typiques du syndrome de Cushing. Six mois

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associated with ectopic ACTH secreting tumour related Cushing syndrome.

Keywords: neuroendocrine tumours, Cushing's syndrome, hyperaldosteronism, hypokalemia.

List of abbreviations:
EAS – ectopic adrenocorticotropic hormone syndrome
EAT – ectopic ACTH-secreting tumour
ABPM – ambulatory blood pressure measurement

auparavant, le même patient a subi une surrénalectomie laparoscopique droite pour hyperaldostéronisme primaire, confirmée par des résultats cliniques, biochimiques, radiologiques et histopathologiques.
Conclusions. Les tumeurs neuroendocrines sont rares, difficiles à diagnostiquer et de mauvais pronostic lorsqu'elles sont associées à un syndrome de Cushing sécrétant de l'ACTH ectopique.

Mots-clés: tumeurs neuroendocrines, syndrome de Cushing, hyperaldostéronisme, hypokaliémie

Introduction

Cushing's syndrome is a rare disorder caused by chronic hypercortisolism with multisystem morbidity, increased mortality and decreased quality of life[1,2]. An ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS) is an infrequent form of endogenous ACTH-dependent Cushing's syndrome[1-3], usually associated with intense hypercortisolism[1-4], as well as severe comorbidities such as hypokalemia, diabetes mellitus, infections and vertebral fractures[1-3,6–9]. EAS is a rare condition, responsible for about 5–20% of all Cushing syndrome cases and 10–20% of ACTH-dependent Cushing syndrome patients[1-4,9–12]. The first time when EAS was named and largely studied was in the early 1960s by Liddle and soon after by Meador[13,14]. In most cases, the source of ectopic production of ACTH is located in the lungs and mediastinum, but it can also be produced by tumours originating from other parts of the body, such as gastroenteropancreatic neuroendocrine tumours, pheochromocytomas and other[1,3,5]. The most frequent cause is probably small-cell lung carcinoma, up to 12% of these cases will have Cushing's syndrome[1,2,3,5,15,16]. The ectopic ACTH syndrome is more common in men, and usually presents after the age of 40 years; it should always be considered, even in children. Identification of the source of ectopic ACTH production remains one of the main difficulties. Surgical excision of ectopic lesion is recommended as the first-line therapy of Cushing syndrome, but not all patients are eligible for surgery[17]. Medical therapy may be introduced to control the cortisol excess when the disease is not definitively cured via resection or there is a surgical contraindication[17,18]. Steroidogenesis inhibitors can block various steps of the steroid synthesis pathway. Since the recommended first line treatment of EAS is the surgical removal of the ectopic ACTH-secreting tumour (EAT)[17], its prompt localization is crucial. However, the first imaging study succeeds in identifying the EAT in only 50–60% of cases, while the ectopic origin of ACTH may remain occult for several years in up to one-fifth of patients[4,5].

Case presentation

A 21-year-old man presented to the emergency room, reporting palpitations, shortness of breath and headache. While all symptoms were sudden in onset, the patient had never experienced palpitations or any difficulty breathing in the past. He was being managed in an outpatient clinic for hypertension for some months. He has been taking two antihypertensive drugs (amlodipine and enalapril). The patient denied relevant pathological medical history including smoking, alcohol use, or drug consumption, and had no previous hospital admissions. Regarding family history, his father was diagnosed with hypertension at the age of 48 years and chronic kidney disease. No familial hereditary diseases were known. On physical examination, his heart rate was 110 bpm, while his blood pressure was 180/115 mm Hg. Cardiac, abdominal, neurological and musculoskeletal examinations were unremarkable. Initial investigations revealed normal hematological and renal parameters, but showed a serum potassium of 2.6 mmol/L.

Urinalysis returned negative. The chest X-ray and electrocardiogram performed at the time of admission were unremarkable, as well. After the patient was admitted for refractory hypokalaemia, oral and intravenous potassium supplementation was started. However, the patient's potassium remained 2.9 mmol/L. Ambulatory blood pressure measurement (ABPM) provided a profile of blood pressure values out of normal ranges. More than 85% of systolic blood pressure measurements were over 135 mmHg, and 42% of diastolic blood pressure values were over 85 mmHg. The patient underwent a clinical workup, to rule out other causes of secondary hypertension. Serum aldosterone and renin levels were 89 ng/L and 0.17 mIU/L, respectively, and cortisol level was 75 ng/mL. The aldosterone/renin ratio was calculated to be 523 ng/L per mIU/L. The findings of hypokalaemia and increased values of aldosterone/renin ratio suggested the diagnosis of primary aldosteronism. Echocardiography found severe left

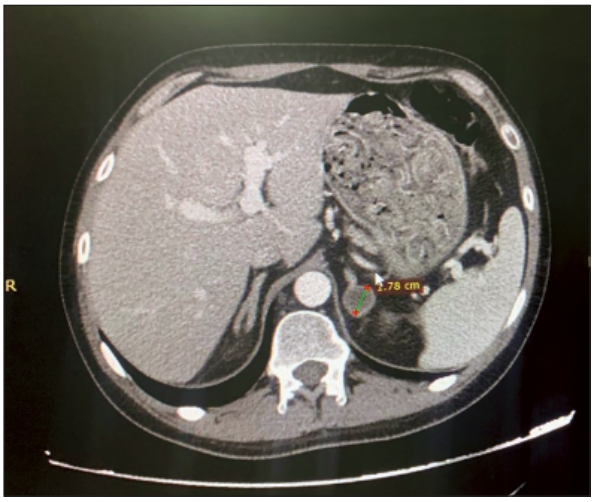


Figure 1. Computed tomography scan of the abdomen



Figure 2. Adrenal adenoma as surgical specimen after adrenalectomy.



Figure 3 (a,b). Striae on patient's arms and abdomen region.

ventricular hypertrophy. A computed tomography scan of the abdomen, with contrast, showed a hypo dense nodule measuring 1.8×1.8 cm in the medial limb of the left adrenal gland (Figure 1), probable a left adrenal adenoma.

The patient was initially treated with oral spironolactone and oral potassium chloride during his hospital stay. By the fifth day of hospitalization, electrolytes and blood pressure had been corrected and he remained on verapamil, doxazosin, and spironolactone. The patient underwent left laparoscopic adrenalectomy (Figure 2), without any complications. The histopathological examination of the surgical specimens revealed an adrenal adenoma. Subsequently, after being discharged, the patient remained normokalemic and normotensive, without any medications.

After several months, the patient presented with complaints of paresthesias in both arms and legs. On arrival, his blood pressure was high (192/112 mm Hg). The physical examination showed obesity (body mass index 31.6 kg/m^2), central adiposity, moon face, and a buffalo hump, wide and purple skin striae on his legs, arms and abdomen (Figure 3 a, b). He also presented pitting edema of both legs, extending to the upper thighs. The patient gained over 10 kg of weight, after the first intervention. Other clinical findings were normal. There was no history of corticosteroid use. The family history was significant for chronic kidney disease, without family history of endocrine tumours. The biochemical tests at admission indicated mild hyponatremia (135 mmol/L) and severe hypokalemia (2.6 mmol/L), together with metabolic alkalosis. Calcemia, phosphatemia, and magnesemia were all within normal limits. We initiated a protocol for the detection of endocrine hypertension, including tests for Cushing's syndrome. The morning cortisol level was 375 ng/mL (normal range 55-200 ng/mL), cortisol at 4 p.m. was 348 ng/mL (normal range 28-140 ng/mL), and ACTH level 189 pg/mL (normal range 8-65 pg/mL), without changes in other pituitary hormones. Cortisol failed to suppress during an overnight dexamethasone suppression test (a single dose of 8 mg of dexamethasone). The MRI examination of the pituitary region was

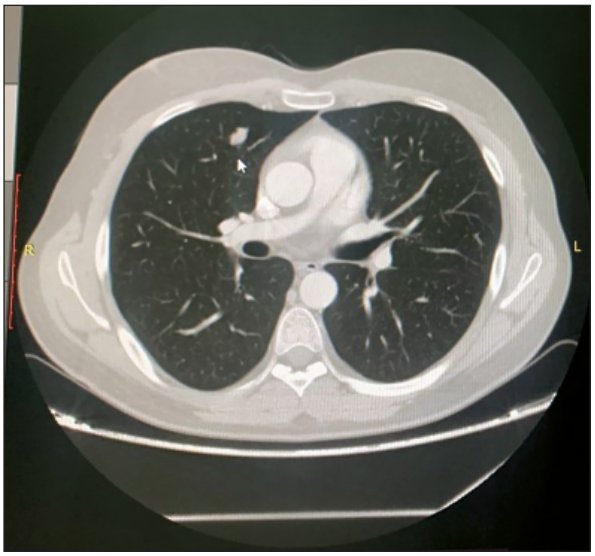


Figure 4. Computed tomography scan of chest. Nodule in the right superior lung lobe.



Figure 5. Tumour macroscopic specimen after thoracic surgery.

normal. Chest computed tomography scan showed a lung nodule of 1.1 cm located in the right superior lob (Figure 4). The bronchoscopic examination was normal. Abdominal computed tomography revealed hyperplasia of the right adrenal gland and an empty cavity of the left adrenal gland. The clinical and radiological findings supported the diagnostic hypothesis of ectopic ACTH-dependent Cushing's syndrome.

Hypokalemia persisted, requiring a high intravenous K supply (up to 260 mEq per day), and arterial hypertension could not be effectively controlled despite the administration of enalapril/ amlodipine/ spironolactone. We initiated oral fluconazole 400 mg per day, to suppress cortisol production. The patient was discharged and continued with the same therapy for two weeks. The case was discussed by a multidisciplinary team that included an endocrinologist, a thoracic surgeon, an anesthesiologist, and a radiologist. It was decided to refer the patient to thoracic surgery, to analyze the pulmonary nodule through the frozen section and then proceed with thoracic surgery, according to the results. The patient accepted the surgery and two weeks later, he underwent invasive thoracic surgery (Figure 5). Frozen section analyses resulted positive for a neuroendocrine tumour. The postoperative course was uneventful, and the patient was discharged on postoperative day 7, in a good clinical condition. The final histopathological examination confirmed the frozen section procedure results: a typical carcinoid tumour (according to the World Health Organization 2015 classification), strongly positive for ACTH immunostaining. After surgery, low levels of morning plasmatic ACTH and cortisol (ACTH 10.67 pg/mL, cortisol 60 ng/mL) confirmed EAS remission. In the following days, the general clinical status of the patient significantly improved. Three months after surgery, a biochemical evaluation showed a persistent remission of the disease, and the signs and symptoms of Cushing's syndrome were resolved.

Discussion

The clinical manifestations in Cushing's syndrome result from a chronic exposure to excess glucocorticoids. Patients with the ectopic ACTH syndrome usually present with severe and rapidly developing metabolic signs, most prominently anorexia, myopathy and glucose intolerance. Because of severe hypercortisolemia and additional mineralocorticoid effect, hypokalemic alkalosis is found, with peripheral oedema on clinical examination[21]. Patients with ACTH-producing bronchial carcinoids tend to develop all of the typical Cushingoid features, complicating its differentiation from Cushing's disease. The distribution of fat can be useful, as typically in Cushing's syndrome there is truncal obesity, "moon face", "buffalo hump", and supraclavicular fat pads[4, 9]. Other signs are proximal myopathy, wide purple striae, osteoporosis, thin skin and easy bruising. Our patient presented with hypertensive crisis associated with hypokalemia and had some of these features suggestive for hypercortisolism.

In patients with clinical findings suggestive of Cushing's syndrome and ACTH-dependent hypercortisolism, the diagnostic challenge is to differentiate an occult ectopic ACTH-producing tumour from an ACTH-producing pituitary microadenoma. Depending on hormone activity and complex

regulation systems, neuroendocrine tumours always are a challenge in diagnosis and treatment[19]. Ectopic ACTH syndrome represents a minority of all cases of Cushing's syndrome[13].

The high-dose dexamethasone test can be used to differentiate ectopic ACTH syndrome from classic Cushing's disease[20]. When data from the literature were analyzed, the sensitivity of the suppression test with 8 mg of oral dexamethasone varied from 65 to 100%, and the specificity from 60 to 100%[8]. In our patient, the cortisol suppression test could be compatible with a diagnosis of ectopic ACTH syndrome. Most cases in the first decades after establishing the definition of EAS were caused by small cell lung carcinomas[11,12]. Still, almost half of the tumours can be found in the thoracic cavity, mostly bronchial carcinoids[3,5]. EAS patients are more likely to experience severe hypokalemia, which has been previously broadly studied: the higher the plasma cortisol concentration, the more severe the hypokalemia[5].

Ketoconazole, a steroid synthesis inhibitor, has previously been used to treat cortisol excess through inhibition of CYP450 enzymes 11-b-hydroxylase and 17-a-hydroxylase, though its availability is limited in many countries[17]. Fluconazole represents a suitable alternative for the medical management of Cushing's disease and shares similar properties to ketoconazole, although it has less associated toxicity[18]. We used fluconazole 600 mg/day to treat our patient, for reducing cortisol levels before intervention. Surgical excision is the ideal curative treatment for EAS[3,7,13]. The ideal candidates for surgery have radiologically visible, well-differentiated bronchial neuroendocrine tumours, that can be readily excised or removed after days to weeks of preparation with pharmacological treatment in patients with a bad general condition[22].

Conclusions

Ectopic Cushing's syndrome is an uncommon cause of hypercortisolism. We should pay attention to the screening of the causes of secondary hypertension. In patients with very small lesions responsible for hormonal syndromes, or difficult location, a high level of suspicion is required to obtain a diagnosis. Multidisciplinary team is needed for a better critical judgement and ideal treatment, which can prolong life expectancy and manage hormonal complications.

Author's Contributions:

E.N. and D.A. conceived and drafted the article. I.K. and J.F. participated in the design of the study. M.T. and A.Y. revised it critically for important intellectual content. A.G. operated the patient for the first time (laparoscopic adrenalectomy) and provided the photographs of surgery. F.G. operated the patient for the second time and provided the photographs of surgery. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient included in the study"

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