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The Diagnostic Challenges in ACTH Dependent Cushing's Disease

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Authors' contributions

This work was carried out in collaboration between all authors. All authors were involved in the medical management of this patient. In addition, authors ETCX and MQM were involved in writing the manuscript. Authors MQM, THA and RELC managed the literature searches. Author ETCX designed the figures and contributed to the correction of the draft. Author RM provided the case, wrote and edited the work. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Objective: To discuss the difficulties in the diagnostic workup and management of ACTH dependent Cushing's syndrome.
Methods: We report the case of a patient with ACTH dependent Cushing's syndrome, in whom the identification of the source of ACTH production was a challenge.
Results: A 26-year-old man presented with a weight gain of 20kg, hypertension (250/160 mmHg), hypokalemia, purple stretch marks and severe proximal muscle weakness 6 months of evolution. He also had 4 episodes of pneumonia requiring hospitalization. ACTH-dependent hypercortisolism (cortisol 32ng/dl, ACTH 135pg/ml) was diagnosed. The severe clinical presentation suggested the

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possibility of ectopic ACTH production. The dexamethasone suppression test (DST) showed no inhibition of cortisol. Whole body octreotide scintigraphy and gallium-68 PET-CT did not show any evidence of ectopic tumor. A pituitary MRI was reported as normal. Bilateral inferior petrosal sinus sampling was carried out and was essential in establishing a diagnosis of Cushing's disease. In a second MRI, a pituitary microadenoma on the left side was identified. The patient underwent transsphenoidal resection. Postoperatively, hypercortisolism persisted, and since the patients clinical condition deteriorated further, bilateral adrenalectomy was successfully performed, providing a definitive cure for the life threatening hypercortisolism.

Conclusion: The diagnosis and management of ACTH dependent Cushing´s syndrome remains a challenge. The results of dexamethasone suppression tests should be evaluated in the context of the patient. These tests have a high negative predictive value; however in the context of critical illness (pneumonia) may alter the hypothalamic-pituitary-adrenal axis response. This case confirms the need for a bilateral IPS sampling in order to establish diagnosis.

Keywords: Cushing's disease; ectopic Cushing's syndrome; pituitary microadenoma; bilateral inferior petrosal sinus.

1. INTRODUCTION

The differential diagnosis of ACTH-dependent Cushing's syndrome includes adrenocortico-trophic hormone (ACTH)–secreting pituitary adenoma (Cushing´s disease) and ectopic ACTH syndrome (a non-pituitary tumor secreting ACTH). About 90% of patients have Cushing's disease; this should be considered the first option in the differential diagnosis. The usual biochemical presentation of ACTH secreting pituitary adenomas is with mild to moderate hypercortisolism, normal or elevated plasma ACTH and normokalemia. In contrast, ectopic ACTH-secreting tumors, often present with rapid onset of hypercortisolism, hypokalemia and a marked elevation in plasma ACTH levels [1].

We describe a case of Cushing's disease attributable to a pituitary microadenoma, with initial clinical and laboratory findings suggestive of ectopic Cushing's syndrome

2. CASE PRESENTATION

A 26-year-old man presented with a six month history of weight gain (20kg) accompanied by prominent purple striae over the abdomen and thighs (Fig. 1). He had facial plethora, hirsuitism, dorsocervical fat and no evidence of hyperpigmentation. He reported marked muscle weakness, easy bruising after minimal injury, arterial hypertension and diabetes mellitus. He was referred to our hospital following two episodes of pneumonia in the previous 4 months, both requiring prolonged hospital stays. His most recent blood tests showed hypokalemia and a serum ACTH of 255 pg/ml. Magnetic resonance imaging (MRI), carried out in another center two months previously, did not report a pituitary lesion. Our task was to investigate the cause of the ACTH dependent hypercortisolism.

Physical examination revealed hypertension (250/160 mmHg), a typical cushingoid appearance with significant proximal muscle wasting and weakness. Laboratory tests revealed severe hypokalemia (K=2.7 mEq), hyperglycemia (glucose 181 mg/dl), metabolic alkalosis and elevated basal ACTH, serum cortisol and urinary free cortisol levels (135 pg/mL, 32.4 ug/dl and 2,079 ug/24hr, respectively).

The clinical picture was suggestive of ectopic Cushing's syndrome (rapid onset of symptoms, marked hypokalemia and proximal myopathy). In order to differentiate between a pituitary and an ectopic source of ACTH, a 7 hour continuous dexamethasone infusion test was carried out; no inhibition occurred on the second day, supporting the possibility of ectopic ACTH production. A thoracic CT scan was performed and the only finding was pneumonia. This was treated with intravenous antibiotics, but the patient required ventilator support in the intensive care unit for several days.

He recovered from this third episode of pneumonia and our search for the source of hypercortisolism continued. Bilateral inferior petrosal sinus (IPS) catheterization was considered, but experience in our center had been limited due to the high cost of this diagnostic modality. The clinical picture appeared to be more compatible with ectopic ACTH production, priority was given to radiological imaging to search for a neuroendocrine tumor. In

addition, the patient was commenced on ketoconazole 800 mg a day which was later increased to 1200 mg a day, in order to block adrenal cortisol production. This was well tolerated and the patients' peripheral edema, high blood pressure and diabetes rapidly improved. The patient underwent triphasic CT scanning and whole body octreotide scintigraphy; both failed to demonstrate a neuroendocrine tumor.

Due to these negative findings, we repeated the cranial MRI scan (about 30 days after the first scan) and a pituitary microadenoma (5x6 mm) (Fig. 2) on the left side of the gland was reported. This tumor had not been described in the first scan. As a result of this, IPS catheterization with desmopressin stimulation (10 mcg IV) was programmed; cosyntropin is not available in our country. The procedure was successfully carried out and showed clear lateralization to the left (Table 1).

The cause of this patient's hypercortisolism was therefore confirmed due to an ACTH-secreting pituitary adenoma. He underwent trans-sphenoidal surgery to extirpate the tumor. The pathology report mentioned partial resection of the adenoma. After surgery hypercortisolemia persisted and despite the re-initiation of ketoconazole, the patient's clinical condition worsened. Other pharmacological therapies were considered in this case; however metyrapone is not available in our country, pasireotide was too expensive for the patient and etomidate would have meant moving the patient to a high dependency unit for monitoring, with the associated risk for intubation due to his poor respiratory function.

He developed sinusitis and another episode of hospital acquired multifocal pneumonia. This time he recovered without requiring mechanical ventilation. Due to the history of recurrent life threatening infections, the patient finally underwent bilateral adrenalectomyin order to provide a definitive solution to the hypercortisolism. Postoperatively the patient was started on hydrocortisone and fludrocortisone replacement therapy and discharged home.

Table 1. Inferior petrosal sinus sampling after desmopressin stimulation; peripheral veins (P= femoral vein) and each petrosal sinus (right and left)

Time (min)	ACTH (pg/ml) after desmopressin stimulation			
	Right IPS	Left IPS	P	IPS/P
Baseline (0)	120	1,900	120	15.8
3	115	3,800	110	34.5
5	125	3,200	110	29.1
10	210	3,000	105	28.6

Abbreviations: ACTH = Adrenocorticotropic Hormone; IPS = Inferior Petrosal Sinus; P = Peripheral

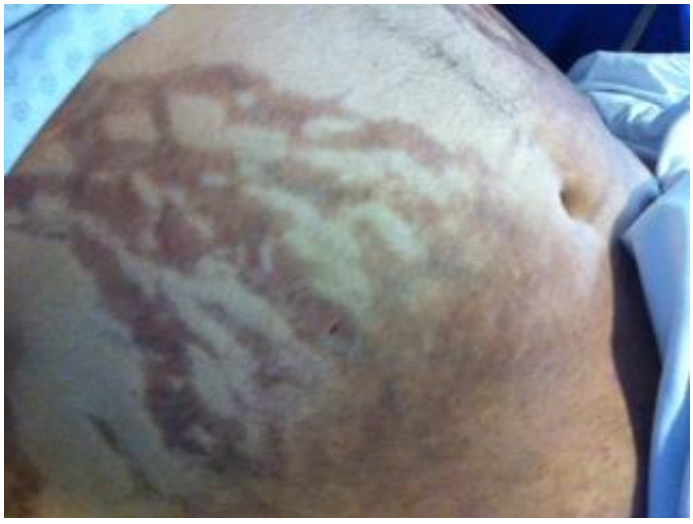

Fig. 1. Multiple wide, violaceous striae on the abdomen of the patient

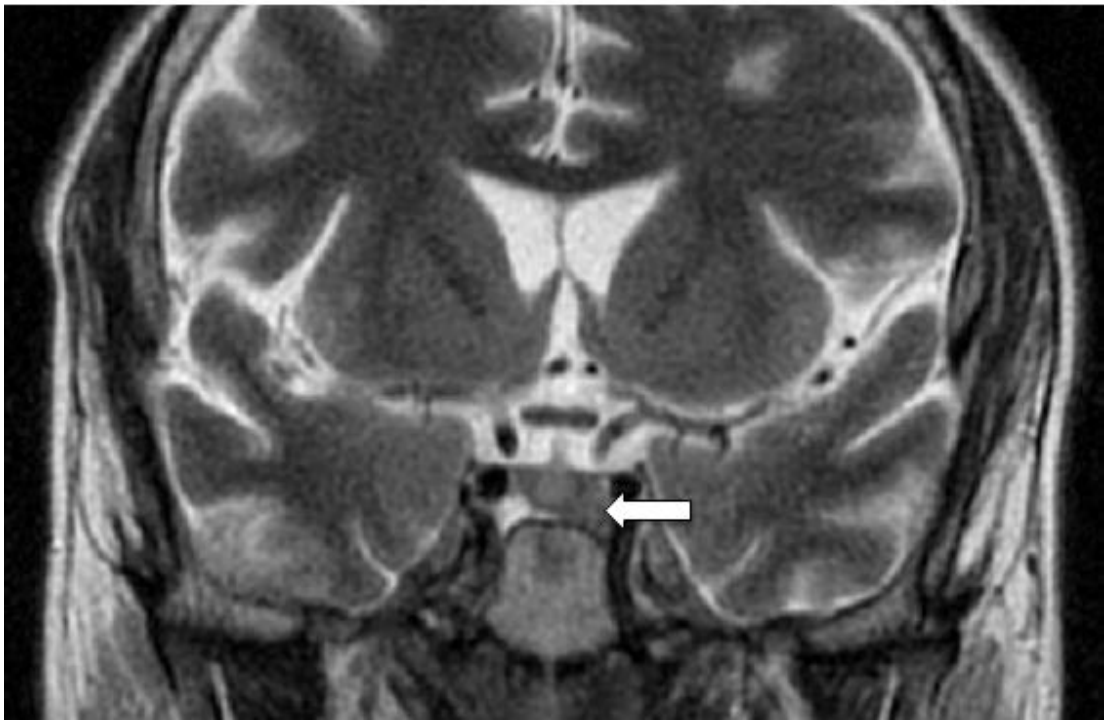

Fig. 2. T2 weighted coronal magnetic resonance image with gadolinium contrast showing a pituitary microadenoma (left side of gland)

3. DISCUSSION

The endogenous causes of hypercortisolism include ACTH-dependent and independent forms of Cushing's syndrome [2]. A corticotrophin pituitary adenoma accounts for 85-90% of patients with ACTH-dependent Cushing's [3]. Such adenomas usually occur between the ages of 25 to 45 years [4]. If a clinical suspicion of endogenous hypercortisolism syndrome exists, a confirmatory biochemical test is needed. These initial tests include either: an elevated 24 hour urinary free cortisol or an elevated night time salivary cortisol or failure of cortisol suppression with the1 mg overnight DST, or the low-dose dexamethasone suppression test (0.5 mg dexamethasone every 6 hours for 48 hours). If these screening tests confirm the biochemical presence of Cushing's syndrome, then plasma ACTH should be measured in order to determine whether this is ACTH-dependent or ACTH-independent [5,6]. In order to differentiate between an ACTH secreting pituitary or ectopic tumor, further dynamic tests need to be carried out. These include the high dose dexamethasone test (2 mg dexamethasone every 6 hours for 48 hours), the 8mg overnight dexamethasone suppression test, CRH testing or the intravenous dexamethasone suppression test. The literature reports that the latter test has a sensitivity of 95%, a specificity of 62% respectively [7].

In our patient, the intravenous dexamethasone suppression test failed to show cortisol suppression, suggesting the possibility of an ectopic ACTH producing tumor. However, DST has a low negative predictive value for excluding Cushing's disease. Furthermore, in retrospect, this dynamic test was performed just 2 days prior to the discovery of hospital acquired pneumonia with acute respiratory failure. Plasma ACTH and cortisol concentrations are frequently elevated in patients with a critical illness. Reincke et al. [8] demonstrated that intensive care unit (ICU) patients have an altered responsiveness to the DST, probably due to a loss of the normal cortisol negative feedback on pituitary ACTH secretion.

Clinical history, biochemistry and physical examination can be useful in discriminating ACTH producing pituitary adenoma from ACTH producing ectopic tumors. Cushing's disease tends to have a gradual onset and usually presents with normal electrolyte values, only 10% of patients present with hypokalemia.

Ectopic ACTH syndrome tends to have a morerapid onset with severe symptomology in particular significant hypokalemia and proximal myopathy [9,10]. The hypokalemia in these patients is due to the saturation of the enzyme 11B-hydroxysteroid dehydrogenase type 2 by excessive cortisol. Normally, this enzyme aids in protecting the mineralocorticoid receptor (MR) from the effects of cortisol [10]. In addition, with time the high ACTH levels provoke hyperpigmentation and patients may have little weight gain. This patient had several features suggestive of an ectopic source i.e. hypokalemia, metabolic alkalosis, severe myopathy, aggressive and rapid onset, high levels of ACTH and no inhibition with the dexamethasone suppression test.

Another feature of this case was the failure to establish the presence of a pituitary adenoma in the initial MRI of the pituitary. For this reason, bilateral IPS catheterization is essential in ACTH dependent cases; especially if there is discordance between clinical, biochemical and / or radiological results [11]. A ratio of IPS to peripheral (IPS/P) ACTH gradient greater than 3 after desmopressin stimulation is diagnostic of Cushing's disease. The sensitivity and specificity of this test is 92.2% and 90% respectively [12,13]. This is an operator dependent procedure, experience is necessary to ensure correct catheterization. This test was delayed in our patient. The principal reason was due to the high cost of this procedure (3000 USD). This was an out of pocket cost for our patient. Secondly, experience with this procedure has been mixed at our center due to operator inexperience.

Once Cushing's disease is diagnosed, transphenoidal adenomectomy or hypophysec-tomy is the first-line treatment option [14]. In this case, the clinical and biochemical features of hypercortisolism persisted postoperatively [15] Success rates range between 69-98% in accordance with the experience of the neurosurgeon. Causes of surgical failure include residual tumor hidden in the gland or the cavernous sinus and ectopic tumor in the parasellar region. Patients who fail this initial surgery can be treated either by repeat transsphenoidal surgery, medical therapy, radiotherapy, or surgical bilateral adrenalectomy [14,16,17].

This patient needed definitive treatment, the hypercortisolism had already resulted in life threatening complications; for this reason, bilateral adrenalectomy was the preferred option [18] Words 712.

4. CONCLUSION

Clinical and biochemical features may not be clear in establishing the diagnosis in ACTH dependent hypercortisolism. In this case, the clinical suspicion of an ectopic lesion seems to have been incorrect. This case was finally diagnosis as ACTH dependent Cushings disease. Nevertheless, we cannot rule out the remote possibility of ectopic ACTH production. However, the IPS test clearly showed lateralization, strongly supporting our diagnosis of Cushings disease.

Bilateral IPS sampling remains the best test for establishing the origin of ACTH secretion and ideally should be carried out in all patients. In addition, patients who have an acute critical illness will probably have an altered hypothalamic-pituitary-adrenal axis. Therefore, results obtained from a DST (which already has a low negative predictive value) may be incorrect- a false negative test is possible. Finally, bilateral adrenalectomy was the necessary and definitive treatment in this patient, despite the localization of the source of ACTH. We are currently following up this patient for the possibility of future Nelsons syndrome.

This case clearly highlights the difficulties in the diagnosis and treatment of ACTH dependent Cushing's syndrome.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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